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 * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:10:30 ON 15 SEP 2005

=> FILE REG

=>
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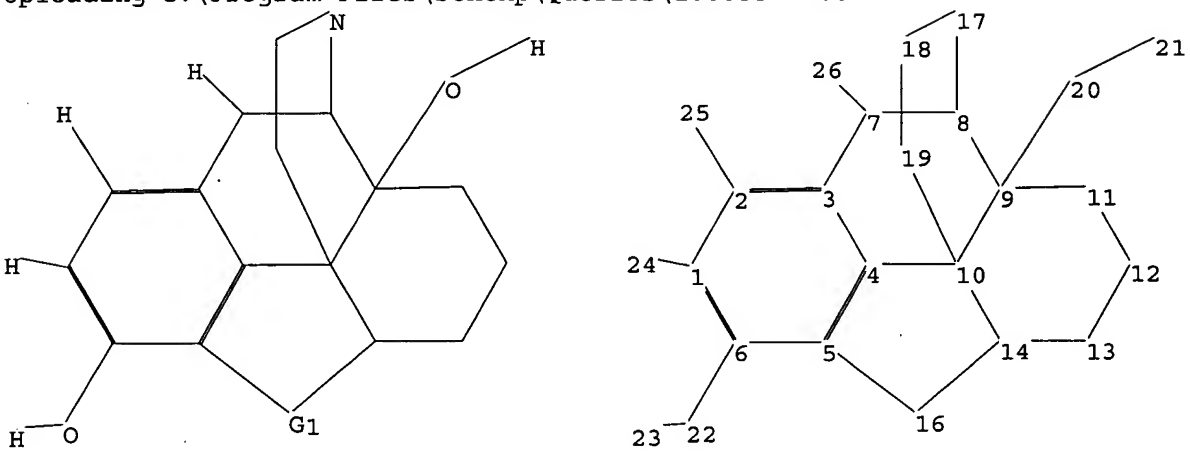


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chain nodes :
20  21  22  23  24  25  26
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12  13  14  16  17  18  19
chain bonds :
1-24  2-25  6-22  7-26  9-20  20-21  22-23
ring bonds :
1-2  1-6  2-3  3-4  3-7  4-5  4-10  5-6  5-16  7-8  8-9  8-17  9-10  9-11  10-14
10-19  11-12  12-13  13-14  14-16  17-18  18-19
exact/norm bonds :
1-24  2-25  3-7  4-10  5-16  6-22  7-8  7-26  8-9  8-17  9-10  9-11  9-20  10-14
10-19  11-12  12-13  13-14  14-16  17-18  18-19  20-21  22-23
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6

G1:O,S,N

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  16:Atom  17:Atom  18:Atom  19:Atom  20:CLASS
21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS



L1       STRUCTURE UPLOADED

=> d l5
L5 HAS NO ANSWERS
L5                STR
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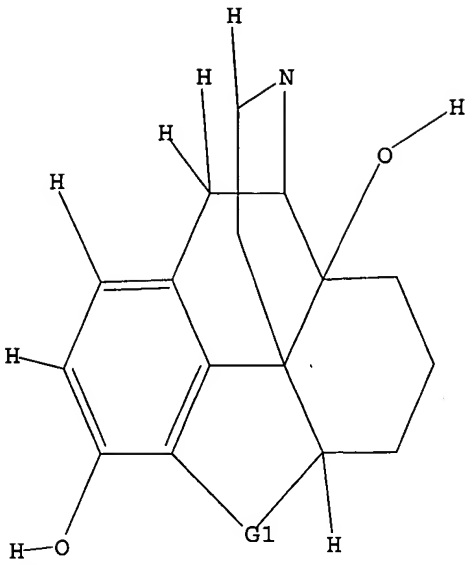


G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.

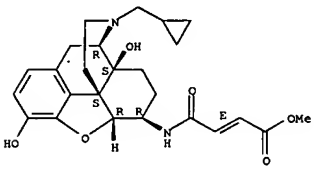
=> s l5 full
L6 2397 SEA SSS FUL L5

=> file ca

=> d ibib abs fhitstr 1-66

L12 ANSWER 1 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 138:331167 CA
TITLE: From Models to Molecules: opioid receptor dimers, bivalent ligands, and **selective** opioid receptor probes. {Erratum to document cited in CA135:116529}
AUTHOR(S): Portoghese, Philip S.
CORPORATE SOURCE: Department of Medicinal Chemistry College of Pharmacy, University of Minnesota, Minneapolis, NM, 55455, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(22), 3758
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On pages 2266 and 2267, two double bonds at the 8,14 and 5,13 positions were erroneously included in ring C of structures 17-19.
IT **72782-05-9**, β-Funaltrexamine
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(opioid receptor dimers, bivalent ligands, and **selective** opioid receptor probes structure activity relationship, mol. modeling and mol. recognition (Erratum))
RN 72782-05-9 CA
CN 2-Butenoic acid, 4-[[(5α,6β)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]amino]-4-oxo-, methyl ester, (2E)- (9CI) (CA INDEX NAME)

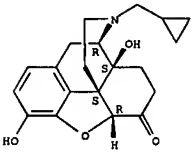
Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 2 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 137:72594 CA
TITLE: Naltrexone potentiates anti-HIV-1 activity of antiretroviral **drugs** in CD4+ lymphocyte cultures
AUTHOR(S): Gekker, Genya; Lokensgard, James R.; Peterson, Phillip K.
CORPORATE SOURCE: Institute for Brain and Immune Disorders, Minneapolis Medical Research Foundation, Hennepin County Medical Center, the University of Minnesota Medical School, Minneapolis, MN, 55404, USA
SOURCE: Drug and Alcohol Dependence (2001), 64(3), 257-263
CODEN: DADEDV; ISSN: 0376-8716
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD4+ T lymphocytes are the primary cell target for human immunodeficiency virus-1 (HIV-1), and these cells are known to express opioid receptors. Due to the need for new treatment approaches to HIV-1 infection, we sought to determine whether the non-**selective** opioid receptor antagonist naltrexone would affect HIV-1 expression in CD4+ lymphocyte cultures and whether naltrexone would alter the antiviral properties of zidovudine (AZT) or indinavir. Activated CD4+ lymphocytes were infected with a monocytotropic or T-cell tropic HIV-1 isolate, and p24 antigen levels were measured in supernatants of **drug**-treated or untreated (control) cultures. While naltrexone alone did not affect HIV-1 expression, at a concentration of 10-12-10-10 M naltrexone increased the antiviral activity of AZT and indinavir 2-3-fold. Similar findings with a κ-opioid receptor (KOR) **selective** antagonist supported the possible involvement of KOR in naltrexone's potentiation of the antiretroviral **drugs**. The results of this in vitro study suggest that treatment of alc. or **opiate** dependent HIV-1-infected patients with naltrexone is unlikely to interfere with the activity of antiretroviral **drugs**. Also, based upon naltrexone's safety profile and its synergistic activity in vitro, these findings suggest clin. trials should be considered of naltrexone as an adjunctive therapy of HIV-1 infection.
IT **16590-41-3**, Naltrexone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(naltrexone potentiates anti-HIV-1 activity of antiretroviral **drugs** in CD4+ lymphocyte cultures)
RN 16590-41-3 CA
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 2 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

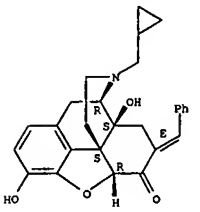


REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 136:15455 CA
TITLE: Heterodimerization of μ and δ opioid receptors: a role in **opiate** synergy
AUTHOR(S): Gomes, I.; Jordan, B. A.; Gupta, A.; Trapaidze, N.; Nagy, V.; Devi, L. A.
CORPORATE SOURCE: Departments of Pharmacology and Anesthesiology, New York University School of Medicine, New York, NY, 10016, USA
SOURCE: Journal of Neuroscience (2000), 20(22), RC110/1-RC110/5
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Opiate** analgesics are widely used in the treatment of severe pain. Because of their importance in therapy, different strategies have been considered for making opiates more effective while curbing their liability to be abused. Although most opiates exert their analgesic effects primarily via μ opioid receptors, a number of studies have shown that receptor-**selective drugs** can enhance their potency. The mol. basis for these findings has not been elucidated previously. In the present study, the authors examined whether heterodimerization of μ and δ receptors could account for the cross-modulation previously observed between these two receptors. The authors find that co-expression of μ and δ receptors in heterologous cells followed by **selective** immunopptn. results in the isolation of μ-δ heterodimers. Treatment of these cells with extremely low doses of certain δ- **selective** ligands results in a significant increase in the binding of a μ receptor agonist. Similarly, treatment with μ- **selective** ligands results in a significant increase in the binding of a δ receptor agonist. This robust increase is also seen in SKNSH cells that endogenously express both μ and δ receptors. Furthermore, the authors find that a δ receptor antagonist enhances both the potency and efficacy of the μ receptor signaling; likewise a μ antagonist enhances the potency and efficacy of the δ receptor signaling. A combination of agonists (μ and δ receptor **selective**) also synergistically binds and potentiates signaling by activating the μ-δ heterodimer. Taken together, these studies show that heterodimers exhibit distinct ligand binding and signaling characteristics. These findings have important clin. ramifications and may provide new foundations for more effective therapies.
IT **153611-34-8**, BNTX
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(opioid μ and δ receptors heterodimers ligand binding and signaling mechanisms in relation to **opiate** synergy)
RN 153611-34-8 CA
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-7-(phenylmethylene)-, (5α,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L12 ANSWER 3 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

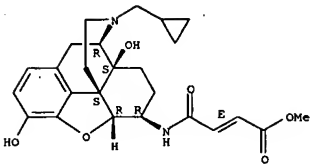


REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 4 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 135:116529 CA
TITLE: From Models to Molecules: Opioid Receptor Dimers, Bivalent Ligands, and **Selective** Opioid Receptor Probes
AUTHOR(S): Portoghese, Philip S.
CORPORATE SOURCE: Department of Medicinal Chemistry College of Pharmacy,
University of Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(14), 2259-2269
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Opiates have been the most widely investigated class of natural products. The development of totally synthetic analgesics subsequently led to the development of diverse structural classes of ligands that mimic the actions of the opiates. Compds. with mixed agonist-antagonist activity during that period represented a new approach to reducing the abuse potential and some of the side effects associated with the classical opiates, and several of the analgesics in this group are presently employed clin. In this presentation I will draw on selected examples from my research to illustrate how key conceptual models have led to the design of **selective** ligands, some of which are widely employed as **pharmacol.** tools for the investigation of opioid receptors. I will also illustrate how site-directed mutagenesis, when combined with the classical structure-activity relationship (SAR) approach, has led to the identification of amino acid residues on opioid receptors and groups on ligands that participate in mol. recognition.
IT 72782-05-9, β-Funaltrexamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(opioid receptor dimers, bivalent ligands, and **selective** opioid receptor probes structure activity relationship, mol. modeling and mol. recognition)
RN 72782-05-9 CA
CN 2-Butenoic acid, 4-[[(5α,6β)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]amino]-4-oxo-, methyl ester, (2E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L12 ANSWER 4 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

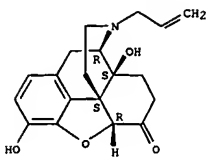


REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 5 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:202960 CA
TITLE: Antagonistic effects of naloxone and naloxonazine on sufentanil-induced antinociception and respiratory depression in rats
AUTHOR(S): Verborgh, C.; Meert, T. F.
CORPORATE SOURCE: Departement Anesthesiologie, Akademisch Ziekenhuis Vrije Universiteit Brussel, Brussels, B-1090, Belg.
SOURCE: Pain (1999), 83(1), 17-24
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several binding studies in rodent brain homogenates have revealed two distinct μ- **opiate** binding sites based on differences in binding affinity of several **opiate** peptides and **opiate** alkaloids. Naloxonazine (NLZ), which preferentially binds to the high affinity μ1 sites, is often used to discriminate between **pharmacol.** effects mediated by μ1 and μ2 binding sites. The present series of expts. were undertaken to compare the opioid antagonistic properties of naloxonazine and naloxone (NLX) (a non-**selective** μ1-antagonist) on i.v. and intrathecal (i.t.) sufentanil (SUF)-induced antinociception and respiratory depression. The opioid antagonists were given either i.v. at 5 min after SUF, or s.c. 24 h prior to the opioid. I.v. NLX and NLZ reduced the i.v. and i.t. SUF-induced antinociception, hypercapnia and hypoxia when given directly after the opioid. There were no major differences in activity between both antagonists. Pretreatment with 30 mg/kg NLX did not reverse the i.v. or i.t. SUF-induced antinociception and respiratory depression. S.c. pretreatment with doses up to 30 mg/kg NLX only partially antagonized the i.v. SUF-induced antinociception, while a complete reversal was present of the opioid-induced hypercapnia and hypoxia. With regard to i.t. SUF, doses up to 30 mg/kg NLZ were unable to reduce the antinociception. The respiratory depression was partially affected; with 30 mg/kg NLZ, the i.t. SUF-induced hypercapnia returned to baseline levels, whereas the SUF-induced hypoxia was only minimally affected. These results challenge the classical view of the selectivity of NLZ for the high affinity μ1 binding sites. They further fail to conform an exclusive role for μ2 receptor sites in the respiratory depression and spinal analgesia induced by a strong lipophilic opioid such as SUF in rats.
IT 465-65-6, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antagonistic effects of naloxone and naloxonazine on sufentanil-induced antinociception and respiratory depression in rats)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

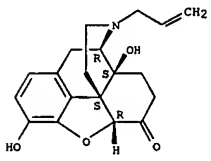
Absolute stereochemistry.

L12 ANSWER 5 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 6 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.



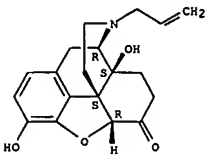
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 6 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 132:175720 CA
TITLE: Prevention of precipitated withdrawal symptoms by activating central cholinergic systems during a dependence-producing schedule of morphine in rats
AUTHOR(S): Buccafusco, Jerry J.; Zhang, Lu C.; Shuster, Laura C.; Jonnala, Ramamohana R.; Gattu, Mahanandeeshwar
CORPORATE SOURCE: Alzheimer's Research Center, Department of Pharmacology and Toxicology, Medical College of Georgia, Augusta, GA, 30912-2300, USA
SOURCE: Brain Research (2000), 852(1), 76-83
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies in this and other labs. have suggested an important role for central cholinergic neurons in the expression of morphine withdrawal symptoms. This study was designed to determine whether the symptoms of withdrawal could be mitigated by normalization of the effect of morphine on cholinergic neurons. Since this effect is generally inhibitory, we used centrally acting cholinergic agonists to augment central cholinergic tone during chronic morphine infusion. Rats were made dependent following the intra-arterial (i.a.) infusion of increasing concns. (35-100 mg kg-1 day-1) of morphine over 5 days. I.a. injection of 0.5 mg/kg of naloxone precipitated a profound withdrawal response that included a dramatic increase in mean arterial pressure (MAP) which was maintained over the 60-min observation period, a short duration increase in heart rate (HR), and characteristic **opiate** withdrawal symptoms. In sep. groups of rats, non-toxic doses (50 and 250 μg/kg) of the acetylcholinesterase (AChE) inhibitor, diisopropylfluorophosphate (DFP) were administered as single daily injections concomitant with the morphine infusion. DFP treated rats, exhibited significantly reduced expression of the naloxone-evoked pressor response. The apparent anti-withdrawal effect of DFP was not reproduced by the **selective** peripherally acting AChE inhibitor, echothiophate, although both compds. effectively reduced the expression of certain other withdrawal symptoms. The centrally acting muscarinic cholinergic receptor agonist, arecoline, resulted in an even more impressive suppression of withdrawal symptoms. While not all symptoms associated with morphine withdrawal are mediated via central cholinergic pathways, these results suggest that phys. dependence on morphine can be suppressed to a significant degree by the augmentation of central cholinergic activity during morphine administration.
IT **465-65-6**, Naloxone
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(precipitated withdrawal symptoms prevention by activating central cholinergic systems during morphine dependence)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

L12 ANSWER 7 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:76407 CA
TITLE: Delta **opiate** receptors account for the castration-induced unmasking of gonadotropin-releasing hormone binding sites in the rat pituitary
AUTHOR(S): Leblanc, Pierre; Heritier, Andree L.; Kordon, Claude
CORPORATE SOURCE: Unite Recherche Dynamique Systemes Neuroendocriniens, UNSERM U159, Paris, F-75014, Fr.
SOURCE: Neuroendocrinology (1998), 68(6), 386-394
CODEN: NUNDAJ; ISSN: 0028-3835
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Under control incubation conditions, gonadotropin-releasing hormone (GnRH) binds only a fraction of its receptors in rat-cultivated pituitary cells. Unmasking of the remaining receptors, which were termed "cryptic", requires **drug**- or peptide-induced protein kinase activation. Spontaneous masking however is not observed on pituitary cells sampled from castrated male rats, suggesting the presence of an intrinsic unmasking factor. Many endogenous factors could theor. account for the effect. It was attempted to identify the factor involved by taking advantage of their differential dependency upon 2nd messengers and transduction cascades. Spontaneous unmasking of GnRH binding was found reversed by pertussis toxin (PTX), an inhibitor of αi and αo subunits of heterotrimeric G proteins, and by U73122, a phospholipase C (PLC) inhibitor. In contrast, desensitization of protein kinase C (PKC) or inhibition of tyrosine kinase by herbimycin were ineffective. Among endogenous pituitary factors able to unmask GnRH receptors in pituitary cells from normal male rats, as epidermal growth factor, neuropeptide Y, or **opiate** peptides, only the latter were found to correspond to this transduction profile. In an attempt to characterize the **pharmacol.** of **opiate** effects, naloxone (10 μM), a poorly **selective opiate** antagonist, restored masking of GnRH binding in cells from castrates. Only the δ antagonist naltrindole (1 μM) was able to mimic the action of naloxone. Conversely, when tested on cells from intact animals, morphine (10 μM), dslet (1 μM), and met-ENK (10 nM), preferential δ agonists, but not dago and β-endorphin or U50488 H and dynorphin, resp. μ and κ agonists, were able to suppress masking. Among opioid peptides endogenous to the pituitary, only met-ENK was able to unmask cryptic receptors, an effect antagonized by naltrindole. The authors conclude that an **opiate** δ receptor subtype is endogenously activated in the pituitary of castrated male rats to prevent masking of GnRH binding.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of naloxone on expression of pituitary GnRH receptors in castrated rats)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 7 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

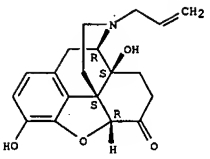


REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 8 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:47336 CA
TITLE: Mechanism of action of the drugs influencing the cough reflex
AUTHOR(S): Nosalova, G.
CORPORATE SOURCE: Ustav Farmakologie, Jessenius Lek. Fakulta, Martin, 03753, Slovakia
SOURCE: Bratislavske Lekarske Listy (1998), 99(10), 531-535
CODEN: BLLIAX; ISSN: 0006-9248
PUBLISHER: Slovak Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: Slovak
AB The role of receptor systems in the activity of antitussive drugs (tramadol, tilidine, pentazocine, codeine, butorphanol) was studied in nonanesthetized cats. The drugs were given i.p. at 10 mg/kg body weight Cough was induced by mech. stimulation of the airways. Decreased cough parameters were noted after administration of all 5 drugs acting on different opiate receptor types. Naloxone pretreatment inhibited the antitussive activity of codeine. Selective antagonist of the 5-HT2 receptors ketanserine given at 1 mg/kg decreased the antitussive effects of codeine by 10% and tramadol by 20%. The ability of codeine to decrease the cough parameters was not altered by pretreatment with haloperidol at 0.1 mg/kg, while reserpine pretreatment decreased the cough-suppressing effects of codeine. The GABAergic agent gabalid strongly decreased the cough parameters. Thus, GABAergic mechanisms may be involved in the mechanism of action of narcotic antitussives agents. Inhibition of glutamatergic synaptic transmission afferent impulses from cough receptors with dextromethorphan suppressed the cough reflex in cats. Thus, the antitussive activity of the tested drugs is not mediated exclusively by μ-opiate receptors. GABAergic and serotoninergic systems and NMDA receptors may also play an important role in the mechanism of action of antitussive drugs. Decrease in brain levels of monoamines may modify the cough-depressant effect of codeine.
IT 465-65-6, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antitussive drugs mechanism of action and role of receptor systems)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

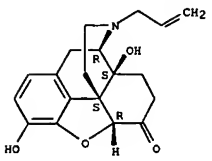
L12 ANSWER 8 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 9 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 130:11475 CA
TITLE: Extinction of ethanol-induced conditioned place preference and conditioned place aversion: effects of naloxone
AUTHOR(S): Cunningham, Christopher L.; Henderson, Carly M.; Bormann, Nancy M.
CORPORATE SOURCE: Department of Behavioral Neuroscience and Portland Alcohol Research Center, The Oregon Health Sciences University, Portland, OR, 97201-3098, USA
SOURCE: Psychopharmacology (Berlin) (1998), 139(1/2), 62-70
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four expts. examined the effect of naloxone pretreatment on the expression and extinction of ethanol-induced conditioned place preference (expts. 1, 2, 4) or conditioned place aversion (expts. 1, 3). DBA/2 J mice received four pairings of a distinctive tactile (floor) stimulus (CS) with injection of ethanol (2 g/kg) given either immediately before or after 5-min exposure to the CS. A different stimulus was paired with injection of saline. Pre-CS injection of ethanol produced conditioned place preference, whereas post-CS injection of ethanol produced conditioned place aversion. Both behaviors extinguished partially during repeated choice testing after vehicle injection. Naloxone (10 mg/kg) had little effect on the initial expression of conditioned place preference, but facilitated its extinction. Moreover, repeated naloxone testing resulted in the expression of a weak conditioned place aversion to the CS that initially elicited a place preference. In contrast, naloxone (1.5 or 10 mg/kg) enhanced expression of conditioned place aversion, thereby increasing its resistance to extinction. A control experiment (experiment 4) indicated that repeated testing with a different aversive drug, lithium chloride, did not affect rate of extinction or produce an aversion to the CS previously paired with ethanol. These findings do not support the suggestion that naloxone facilitates the general processes that underlie extinction of associative learning. Also, these data are not readily explained by the conditioning of place aversion at the time of testing. Rather, naloxone's effects appear to reflect a selective influence on maintenance of ethanol's conditioned rewarding effect, an effect that may be mediated by release of endogenous opioids. Overall, these findings encourage further consideration of the use of opiate antagonists in the treatment of alcoholism.
IT 465-65-6, Naloxone
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(effects of naloxone on ethanol-induced conditioned place preference and conditioned place aversion)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 9 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

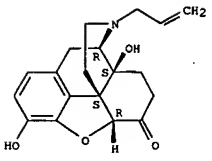


REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 10 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 127:215020 CA
TITLE: Effect of adenosine receptor agonists and antagonists on the expression of **opiate** withdrawal in rats
AUTHOR(S): Salem, Abdallah; Hope, Wendy
CORPORATE SOURCE: School of Pharmaceutical Biology and Pharmacology, Victorian College of Pharmacy, Monash University, Parkville, 3052, Australia
SOURCE: Pharmacology, Biochemistry and Behavior (1997), 57(4), 671-679
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the **selective** A1 adenosine receptor agonist N6-cyclopentyladenosine (CPA) and the **selective** A2a agonist 2-(p-(2-carboxethyl)phenylethyl-ethylamino)-5'-ethylcarboxamidoadenosine (CGS 21680) (each at 0.03, 0.1 and 0.3 mg/kg, SC) as well as the **selective** A1 adenosine receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), non-**selective** antagonists 3-isobutyl-1-methylxanthine (IBMX), aminophylline, 3,7-dimethyl-1-propargyl-xanthine (DMPX) and 8(p-sulfophenyl)-theophylline (8-SPT) were investigated (each at 5, 10 and 30 mg/kg, SC) for their ability to alter the naloxone-precipitated **opiate** withdrawal syndrome in morphine-dependent rats. Effects of CPA and CGS 21680 on **opiate** withdrawal in the presence of aminophylline were also investigated. Both CPA and CGS 21680, caused a significant reduction in the incidence of body shakes, teeth chatter and paw shakes and decreased the amount of fecal matter produced. DPCPX, IBMX, DMPX, 8-SPT and aminophylline significantly increased the incidence of jumps and decreased the amount of fecal matter produced. The incidence of body shakes was significantly increased by DMPX, 8-SPT and IBMX. Neither CPA nor CGS 21680 were able to reverse the significant increase in the incidence of jumps caused by aminophylline. These data suggest that there is a role for endogenous adenosine in the modulation of the **opiate** abstinence syndrome and both A1 and A2a adenosine receptors are involved in this phenomenon.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of adenosine receptor agonists and antagonists on expression of **opiate** naloxone-precipitated withdrawal in rats)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 10 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

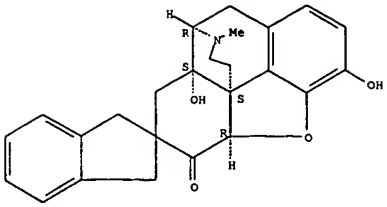


REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 11 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 127:199610 CA
TITLE: 7-Spirobenzocyclohexyl Derivatives of Naltrexone, Oxymorphone, and Hydromorphone as **Selective** Opioid Receptor Ligands
AUTHOR(S): Fang, Xinqin; Larson, Dennis L.; Portoghese, Philip S.
CORPORATE SOURCE: Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Journal of Medicinal Chemistry (1997), 40(19), 3064-3070
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB On the basis of previous structure-activity studies of the highly potent and **selective** δ-opioid receptor antagonist naltrindole and spiroindanyl analogs, we have synthesized epimeric pairs of spirobenzocyclohexyl derivs. of naltrexone, oxymorphone, and hydromorphone. **Pharmacol.** evaluation in smooth muscle assays has revealed that the oxymorphone derivs. are δ- **selective** agonists and possess receptor binding profiles that are consistent with their agonist activity. It is proposed that the spirobenzocyclohexyl group of orients its benzene moiety orthogonally with respect to the C ring of the **opiate** in a manner similar to that of their spiroindanyl analog. It is proposed that this orthogonal orientation serves as an "address" to facilitate activation of δ receptors. The finding that the hydromorphone analogs were full μ agonists and exhibited only partial δ agonist activity suggests that the 14-hydroxyl group also contributes to the δ agonist activity. The naltrexone derivs. were μ- **selective** antagonists and exhibited relatively weak δ antagonist activity. However, the binding data indicated a very high-affinity δ- **selective** binding profile that was not consistent with the **pharmacol.** This study illustrates the differential contributions of the δ "address" to agonist and antagonist activity and supports the idea of different recognition sites for interaction of agonist and antagonist ligands with δ-opioid receptors.
IT **150380-34-0**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(spirobenzocyclohexyl derivs. of naltrexone, oxymorphone, and hydromorphone as **selective** opioid receptor ligands, and preparation thereof)
RN 150380-34-0 CA
CN Spiro[6H-8,9c-(iminoethano)phenanthro[4,5-bcd]furan-6,2'-[2H]inden]-5(4aH)-one, 1',3',7,7a,8,9-hexahydro-3,7a-dihydroxy-12-methyl-, (4aR,7aS,8R,9cS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 11 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

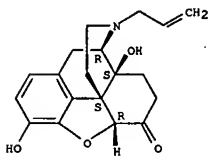


REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L12 ANSWER 12 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:338783 CA
TITLE: Modulation of immunoreactive protein kinase C-α and isoforms and G proteins by acute and chronic treatments with morphine and other **opiate drugs** in rat brain
AUTHOR(S): Ventayol, Pere; Busquets, Xavier; Garcia-Sevilla, Jesus A.
CORPORATE SOURCE: Department Biology, University Balearic Islands, Palma de Mallorca, E-07071, Spain
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1997), 355(4), 491-500
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The abundance of protein kinase C-α and β isoforms (PKC-αβ), PKC-α messenger (m) RNA and guanine nucleotide-binding G protein subunits (Gαi1/2 GαV0 and Gβ) were quantitated in the rat cerebral cortex after acute and chronic treatments with various **opiate drugs**. Acute (100 mg/kg for 2 h) and chronic (10 to 100 mg/kg for 5 days) treatment with morphine decreased similarly the immunoreactivity of PKC-αβ (28% and 32%, resp.). Acute (2 h) and chronic treatment (5 days) with other μ-agonists heroin (30 mg/kg and 10 to 30 mg/kg) and methadone (30 mg/kg and 5 to 30 mg/kg) also induced similar decreases of PKC-αβ (acute: 25 and 23%; chronic: 28 and 18%). After the chronic treatments, spontaneous (48 h) or naloxone (2 mg/kg)-precipitated **opiate** withdrawal (2 h) resulted in up-regulation of PKC-αβ above control levels (30-38%), and in the case of morphine withdrawal in a concomitant marked increase in the expression of PKC-α mRNA levels (2.3-fold). Acute (2 h) treatments with pentazocine (80 mg/kg, mixed κ/δ-agonist and μ-antagonist), spiradoline (30 mg/kg, **selective** κ-agonist) and [D-Pen2, D-Pen5] enkephalin (14 nmol i.c.v., **selective** δ-agonist) induced significant decreases of PKC-αβ (19-33%). Chronic (5 days) treatment with pentazocine (10 to 80 mg/kg), but not spiradoline (2 to 30 mg/kg), also induced a similar decrease of PKC-αβ (35%). In pentazocine- or spiradoline-dependent rats, naloxone (2 mg/kg) did not induce up-regulation of brain PKC-αβ. Acute (10 mg/kg for 2 h) and chronic (2 + 10 mg/kg for 5 and 14 days) treatment with naloxone did not alter PKC-αβ immunoreactivity. Chronic, but not acute, treatment with μ-agonists (morphine, heroin and methadone) increased the immunoreactivities of G αi1/2 (33-37%), Gα0 (25-41%) and Gβ (10-33%) protein subunits. In heroin- and methadone-dependent rats naloxone (2 mg/kg)-precipitated withdrawal (2 h) did not modify the up-regulation of these G proteins induced by chronic μ- **opiate** treatment. In marked contrast to μ-agonists, chronic treatment with high doses of pentazocine and spiradoline or acute treatment with [D-Pen2, D-Pen5] enkephalin did not result in up-regulation of these G protein subunits. PKC-αβ abundance did not correlate significantly with the d. of Gα0. The results indicate that the brain PKC-αβ system may play a major regulatory role in **opiate** tolerance and dependence. Moreover, the possible in vivo

L12 ANSWER 12 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
cross-communication between this regulatory enzyme and specific inhibitory
G proteins may also be of relevance in the cellular and mol. processes of **opiate** addiction.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulation of protein kinase C-α and isoforms and G proteins by treatments with morphine and other **opiate drugs** in rat brain)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



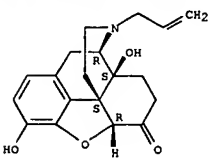
L12 ANSWER 13 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 126:126919 CA
TITLE: Method for terminating methadone maintenance through extinction of the **opiate**-taking responses
INVENTOR(S): Sinclair, John D.
PATENT ASSIGNEE(S): Sinclair, John D., Finland
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5587381	A	19961224	US 1995-410529	19950327

<--
PRIORITY APPLN. INFO.: US 1995-410529 19950327

AB A method is provided for effectively terminating methadone maintenance therapy and the addiction to other legally-available opiates by selectively extinguishing the **opiate**-taking responses. **Selective** extinction is produced having sessions in which detoxified addicts make **opiate**-taking responses while an **opiate** antagonist blocks the pos. reinforcement, interspersed by periods when the antagonist is absent and all responses except **opiate**-taking can be emitted. A similar method but with instructions not to take the **opiate** can subsequently be used to protect against resumption of illegal **opiate** use, or sep. with patients addicted to illegal opiates producing reinforcement through the opioidergic system.
IT **465-65-6**, Naloxone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for methadone maintenance termination through extinction of **opiate**-taking responses)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

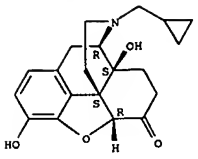
Absolute stereochemistry.



L12 ANSWER 14 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 125:78601 CA
TITLE: Neurobehavioral basis for the **pharmacotherapy** of alcoholism: Current and future directions
AUTHOR(S): Anton, Raymond F.
CORPORATE SOURCE: Department Psychiatry and Behavioral Sciences, Medical
University South Carolina, Charleston, SC, 29425, USA
SOURCE: Alcohol and Alcoholism (**1996**), 31(Suppl. 1), 43-53
CODEN: ALALDD; ISSN: 0735-0414
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 70 refs. Results from studies of **pharmacotherapies** for primary alcoholism are reviewed, including **selective** serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (e.g. fluoxetine), **opiate** antagonists (e.g. naltrexone) and dopamine agonists (e.g. bromocriptine). Because there is considerable comorbidity between alc. dependence, anxiety, and affective disorders, results from studies of medications used to treat these psychiatric disorders are also reviewed, including the 5-HT agonist buspirone and the noradrenergic agent desipramine. The neurobehavioral model of alc. dependence implies that combinations of medications may lead to more effective treatment; thus, identifying subtypes of alc. patients will be important in determining which therapies or combinations of therapy will be most effective in treating alc. dependence. For example, in an ongoing study, we are attempting to subtype an alc. population for treatment selection by measuring endogenous opioid activity. Because endogenous opioids are involved in analgesia, we exposed male and female subjects with alcoholism [some of whom had post-traumatic stress disorder (PTSD)] to cold-induced pain and measured their response before and after administration of naloxone or placebo. The naloxone injection reduced pain response. In addition, women who have PTSD are much more sensitive to stress, which may be related to levels of brain opioid activity.
IT **16590-41-3**, Naltrexone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(current and future directions for neurobehavioral basis for the **pharmacotherapy** of alcoholism in humans)
RN 16590-41-3 CA
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

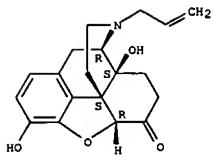
L12 ANSWER 14 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 15 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 124:336130 CA
TITLE: A chimeric analysis of the opioid receptor domains critical for the binding selectivity of μ opioid ligands
AUTHOR(S): Watson, Brendon; Meng, Fan; Akil, Huda
CORPORATE SOURCE: Mental Health Research Institute, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Neurobiology of Disease (**1996**), 3(1), 87-96
CODEN: NUDIEM; ISSN: 0969-9961
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The μ opioid receptor plays a key role in mediating the physiol., **pharmacol.**, and behavioral effects of endogenous opioids and of **opiate drugs** such as morphine and heroin. This study examines the structural features critical to the **selective** binding of μ ligands to the μ receptor as opposed to the other two highly homologous opioid receptors, δ and κ. We use a series of chimeric constructs between the μ and either the δ or the κ receptors to investigate the structural bases of binding selectivity of multiple classes of μ- **selective** ligands. Our results demonstrate that a region comprising the sixth transmembrane domain and the third extracellular loop is critical for the μ/κ discrimination by all μ- **selective** ligands. This region is also critical for μ/δ discrimination by the μ antagonists. However, μ agonists, particularly the peptides, exhibit more complex interactions, often relying on the N-terminal region surrounding the first extracellular loop for μ/δ discrimination. Thus, the same μ peptide ligand depends on different parts of the receptor to discriminate between μ and δ receptors on the one hand and μ and κ on the other. In general, antagonists show the most consistent discrimination mechanisms regardless of construct, whereas agonists, particularly peptides, achieve selectivity by interacting with numerous domains of the receptors.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(chimeric anal. of the opioid receptor domains critical for the binding selectivity of μ opioid ligands)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 15 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 16 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 124:307562 CA
TITLE: Method of simultaneously enhancing analgesic potency and attenuating dependence liability caused by exogenous and endogenous opioid agonists
INVENTOR(S): Crain, Stanley M.; Shen, Kefei
PATENT ASSIGNEE(S): Albert Einstein College of Medicine of Yeshiva University, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

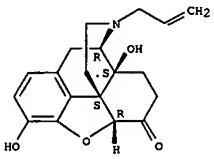
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9602251	A1	19960201	WO 1995-US9974	19950718
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5512578	A	19960430	US 1994-276966	19940719
AU 9532769	A1	19960216	AU 1995-32769	19950718
EP 808165	A1	19971126	EP 1995-929400	19950718
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 10507740	T2	19980728	JP 1995-505298	19950718
US 6011004	A	20000104	US 1996-768221	19961217
AU 9947399	A1	19991028	AU 1999-47399	19990906

PRIORITY APPLN. INFO.:
US 1994-276966 A 19940719
US 1990-612847 B1 19901113
US 1992-947690 B2 19920921
US 1993-97460 A2 19930727
US 1993-153796 A1 19931117
AU 1995-32769 A3 19950718
WO 1995-US9974 W 19950718

AB A method of selectivity enhancing the analgesic potency of morphine and other clin. used bimodally acting opioid agonists and simultaneously attenuating development of phys. dependence, tolerance, and other undesirable side effects caused by chronic administration of these bimodally acting opioid agonists comprises coadministration of a bimodally acting opioid agonist which activates both inhibitory and excitatory

L12 ANSWER 16 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
opioid receptor-mediated functions of neurons in the nociceptive (pain) pathways of the nervous system and an opioid receptor antagonist which selectively inactivates excitatory opioid receptor-mediated side effects. Excitatory opioid receptor antagonists may be used alone to block the undesirable excitatory side effects of endogenous bimodally acting opioid agonists which may be markedly elevated during chronic pain. A method of long-term treatment of previously detoxified **opiate**, cocaine, and alc. addicts utilizes these excitatory opioid receptor antagonists, either alone or in combination with low-dose methadone, to prevent protracted phys. dependence. Thus, etorphine and dihydroetorphine acted as potent **selective** antagonists at excitatory opioid receptors on mouse dorsal root ganglion explant neurons, thereby enhancing the inhibitory effects of bimodally acting opioid agonists such as morphine and dynorphin. Diprenorphine, naloxone, and naltrexone at low concns. also showed potent **selective** antagonist action at excitatory opioid receptors. Chronic cotreatment of dorsal root ganglion neurons with morphine and ultra-low-dose naloxone or naltrexone prevented development of opioid excitatory supersensitivity (dependence) and tolerance.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(method of simultaneously enhancing analgesic potency and attenuating dependence liability caused by exogenous and endogenous opioid agonists)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

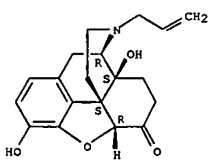
Absolute stereochemistry.



L12 ANSWER 17 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:256185 CA
TITLE: **Pharmacological** antagonism of lipoprivic feeding induced by sodium mercaptoacetate
AUTHOR(S): Garosi, Vittorio L.; Nisoli, Enzo; Blundell, John E.; Carruba, Michele O.
CORPORATE SOURCE: Section of Pharmacology, Toxicology, and Experimental Therapeutics, School of Medicine, University of Brescia, Via Valsabbina 19, Brescia, 25123, Italy
SOURCE: European Journal of Pharmacology (**1995**), 276(3), 285-9
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Drugs**, such as sodium mercaptoacetate and methylpalmoxirate, which block fatty acid oxidation at different levels in the metabolic pathway, stimulate feeding. **Selective** centrally-induced stimulation of dopamine, serotonin (5-hydroxytryptamine, 5-HT) and β-adrenoceptors, or inhibition of the opiatergic system substantially decrease food intake in rats trained to eat 4 h a day. The results of the present study show that centrally acting dopaminergic and serotoninergic anorexic **drugs**, the **opiate** receptor antagonist naloxone, the α-adrenoceptor blocking **drug** phentolamine, and peripherally administered 5-HT counteract the overeating induced by mercaptoacetate. Comparing these effects to those described in 2-deoxy-D-glucose- and insulin-induced feeding, these data support the proposition that distinct neural circuits are involved in the hyperphagic responses to diverse metabolic stimuli.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**pharmacol.** antagonism of lipoprivic feeding induction by sodium mercaptoacetate)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

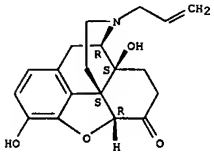
Absolute stereochemistry.



L12 ANSWER 18 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:178238 CA
TITLE: Lesions to terminals of noradrenergic locus coeruleus neurons do not inhibit **opiate** withdrawal behavior in rats
AUTHOR(S): Chieng, B.; Christie, M. J.
CORPORATE SOURCE: Department of Pharmacology, University of Sydney, Sidney, NSW, 2006, Australia
SOURCE: Neuroscience Letters (**1995**), 186(1), 37-40
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The involvement of neurons of the locus coeruleus (LC) in expression of **opiate** withdrawal behavior was tested in morphine-dependent rats using N-2-chloroethyl-N-ethyl-2-bromobenzylamine (DSP4), a neurotoxin **selective** for noradrenergic terminals arising from LC. Lesions were validated by determination of cortical noradrenaline concns. using gas chromatog.-mass spectrometry, inhibition of the post-decapitation hindpaw reflex and dopamine-β-hydroxylase immunohistochem. Lesions did not inhibit the expression of any naloxone-precipitated withdrawal signs. These results suggest no involvement of noradrenergic LC neurons in expression of the overt signs of **opiate** withdrawal, and raise the possibility that previous microinjection and electrolytic lesion studies were confounded by effects on nearby brain regions.
IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(lesions to terminals of noradrenergic locus coeruleus neurons do not inhibit **opiate** withdrawal behavior in rats)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



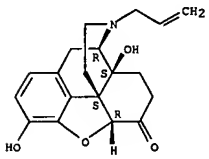
L12 ANSWER 19 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:151716 CA
TITLE: Long-term exposure to opioid antagonists up-regulates prodynorphin gene expression in rat brain
AUTHOR(S): Romualdi, Patrizia; Lesa, Giovanni; Donatini, Alessandra; Ferri, Sergio
CORPORATE SOURCE: Department of Pharmacology, University of Bologna, via Irnerio 48, Bologna, 40126, Italy
SOURCE: Brain Research (1995), 672(1-2), 42-7
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors investigated the effect of long-term administration of opioid antagonists on the regulation of prodynorphin gene expression in rat brain. Intracerebroventricular (i.c.v.) injections for seven days of nor-binaltorphimine (nor-BNI), the highly **selective** κ opioid antagonist, naloxone and its longer acting analog naltrexone, both relatively **selective** antagonists for the μ opioid receptor, markedly raised prodynorphin mRNA levels in rat hypothalamus, hippocampus and striatum. Peptides, namely immunoreactive-dynorphin A (ir-dyn A), were unaffected after chronic treatment with all antagonists, in the same tissues. These results, taken together with the previous observations, suggest that chronic opioid antagonists, acting on κ and μ opioid receptors, clearly up-regulate prodynorphin gene expression in discrete rat brain regions, activating its biosynthesis. Moreover, the data support the hypothesis that the endogenous opioid system plays a role in the mechanisms underlying the development of **opiate** tolerance.

IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(long-term exposure to opioid antagonists up-regulates prodynorphin gene expression in rat brain)

RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



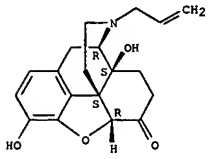
L12 ANSWER 20 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 122:72328 CA
TITLE: Presence in neuroblastoma cells of a μ3 receptor with selectivity for **opiate** alkaloids but without affinity for opioid peptides
AUTHOR(S): Cruciani, Ricardo A.; Dvorkin, Bernyce; Klinger, Harold P.; Makman, Maynard H.
CORPORATE SOURCE: Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Brain Research (1994), 667(2), 229-37
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Evidence is presented for the occurrence of a unique **opiate** alkaloid-**selective**, opioid peptide-insensitive binding site in N18TG2 mouse neuroblastoma cells and in late passage hybrid F-11 cells, derived from N18TG2 neuroblastoma cells and rat dorsal root ganglion cells. Those cells lacked classical opioid peptide-sensitive receptor subtypes, but contained [3H]morphine and [3H]diprenorphine binding sites with affinity for certain **opiate** alkaloids but not for any endogenously occurring opioid peptide or peptide analog tested, including D-ala2-D-leu5-enkephalin (DADLE), D-Ala2,N-Me-Phe4,Gly5-ol (DAGO) and dynorphin A(1-17). The binding site differed from hitherto described μ, δ and κ neuronal opioid receptors not only on the basis of peptide insensitivity, but also on the basis of selectivity and affinities of alkaloids. Saturation expts. with [3H]morphine indicated the presence of a single site with Kd = 49 nM and Bmax = 1510 fmol/mg protein. This novel binding site was not present in F-11 hybrid cells at early passage. Instead the hybrid cells contained conventional opioid receptors (predominantly δ and also μ) capable of binding DADLE and other peptides as well as **opiate** alkaloids. With addnl. passage (cell divisions) of the hybrid cells, during which a limited change occurred in mouse chromosome number, the peptide-insensitive binding appeared and the opioid peptide-binding (δ and μ) receptors were lost reciprocally. Thus, expression of the peptide-insensitive binding normally may be repressed when conventional opioid receptors are expressed. The peptide-insensitive **opiate** binding site described here appears to correspond to the μ3 receptor subtype, recently identified **pharmacol.** and functionally in several cell types of the immune system. It is proposed that this **opiate** alkaloid-sensitive μ3 receptor of macrophages and certain other immunocytes is also present in certain neuronal cell lines and thus may possibly exist in certain neurons of the intact organism.

IT **465-65-6**, Naloxone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alkaloid-sensitive peptide-insensitive μ3-opioid receptor of neuronal cell lines)

RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

L12 ANSWER 20 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.



L12 ANSWER 21 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 121:272189 CA
TITLE: Delta opioid receptor antagonists to block opioid agonist tolerance and dependence
INVENTOR(S): Portoghese, Philip S.; Takemori, Akira E.
PATENT ASSIGNEE(S): Regents of the University of Minnesota, USA
SOURCE: U.S., 13 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5352680	A	19941004	US 1992-914448	19920715
PRIORITY APPLN. INFO.:			US 1992-914448	19920715

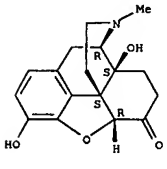
OTHER SOURCE(S): MARPAT 121:272189

AB A therapeutic method is provided to alleviate the tolerance to, or dependence on, an **opiate** analgesic (morphine, codeine, etc.) by the administration of an effective amount of a **selective** δ opioid receptor antagonist (Markush included) to a human patient in need of such treatment. The effect of naltrindole and naltrindole 5'isothiocyanate on μ opioid receptors and on the development of morphine tolerance and dependence in mice chronically treated with morphine are described.

IT **76-41-5**, Oxymorphone
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(δ opioid receptor antagonists to block opioid agonist tolerance and dependence)

RN 76-41-5 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 22 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 121:271946 CA
TITLE: Differential regulation of mu and delta **opiate** receptors by morphine, **selective** agonists and antagonists and differentiating agents in SH-SY5Y human neuroblastoma cells
AUTHOR(S): Zadina, J. E.; Harrison, L. M.; Ge, L.-J.; Kastin, A. J.; Chang, S. L.
CORPORATE SOURCE: Veteran Administration Medical Center, Tulane Univ. Sch. Medicine, New Orleans, LA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1994**), 270(3), 1086-96
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

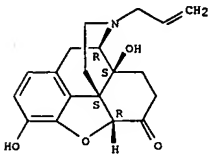
AB Mu and delta **opiate** receptor regulation by **opiate** agonists and antagonists was studied in the human neuroblastoma cell line SH-Sy5Y. Morphine down-regulated both mu and delta receptors, but its effect on each subtype could be dissociated by use of specific antagonists.
The **selective** mu antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Pen-Thr-NH2 (CTAP) blocked the down-regulation of mu, but not delta receptors. Conversely, the delta antagonist {N,N-diallyl-Tyr-Aib9Aib-Phe-Leu-OH({N,N-diallyl-Tyr2,3]Leu-enkephalin)} ICI 174,864 blocked morphine-induced down-regulation of delta but not mu receptors. These **selective** antagonists also were studied alone for their effects on both receptors. CTAP alone at doses of 0.1 μM and higher up-regulated mu receptors. CTAP did not affect delta receptors at 0.3 μM or les, but it down-regulated them at doses of 1 μM or more, apparently due to its delta agonist activity at higher doses, which was reversed by ICI 174,864.
ICI 174,864 alone also showed complex effects on the two subtypes, up-regulating both mu and delta sites. Its effects were most **selective** at a low dose (01. μM), which up-regulated delt sites with minimal effects on mu sites. The nonselective antagonist naloxone provided a more robust up-regulation (>40%) of both mu and delta receptors than either **selective** antagonist alone or in combination. The mu-to-delta ratio (1.4 to 1) was not altered by differentiation of the cells with retinoic acid, which up-regulated both mu and delta receptors. Differentiation with the phorbol agent 12-O-tetradecanoylphorphol-13-acetate, however, up-regulated mu, but not delta receptors. The **selective** mu agonist Tyr-Pro-MePhe-D-Pro-NH2 (PL017) down-regulated mu receptors with a half-maximal effect at 180 nM, but was without effect on delta receptors at concns. up to 10 μM. Conversely, the **selective** delta agonist Tyr-D-Pen-Gly-Phe-D-Pen([D-Pen2,5]-enkephalin) (DPDPE) potently down-regulated delta receptors, producing half-maximal decreases at 0.5 nM. At doses above that reduced the maximum binding of [3H]pCl-DPDPE binding to the delta site, DPDPE also induced an apparent loss of affinity (increased Kd) at the delta site. It was without effect on mu receptor, however, at doses up to 10 μM. Thus, down-regulation of mu and delta receptors was homologous, because **selective** agonist down-regulated their resp. receptors without effect on the heterologous **opiate** receptor. These studies show

L12 ANSWER 22 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
that the use of SH-SY5Y cells in combination with **selective** pharmacol. agents permits the study of **selective** regulation of mu and delta **opiate** receptors, as well as the effect of compds. such as morphine and naloxone, that can affect both receptors in the same cell line.

IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(mu and delta **opiate** receptor regulation by **opiate** agonists and antagonists in human neuroblastoma cell line SH-Sy5Y)

RN **465-65-6** CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 23 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 120:95488 CA
TITLE: Evidence for functional dissociation of dependence and tolerance in guinea pig isolated ileal segments following 20 hour exposure to morphine in vitro
AUTHOR(S): David, C.; Davis, N.; Mason, R.; Wilson, V. G.
CORPORATE SOURCE: Med. Sch., Univ. Nottingham, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Pharmacology (**1993**), 110(4), 1522-6
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

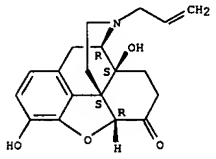
AB In the present study the authors have examined the relationship between tolerance and dependence in isolated ileal segments from the guinea pig under three different conditions: fresh prepns. not previously exposed to morphine (fresh/morphine naive); prepns. and overnight at 4° in modified Krebs-Henseleit saline containing 10 μM morphine and extensively washed with modified Krebs-Henseleit saline to remove residual morphine (overnight-stored/morphine-exposed). Morphine produced a concentration-dependent inhibition of the response of ileal segment to 0.1 Hz, 1 ms and 10 V transmural field stimulation in fresh/morphine-naive, overnight-stored/morphine naive and overnight-stored/morphine exposed prepns. The maximum effect observed was similar in all three prepns. approx. 80% inhibition.
Although, morphine was significantly more potent in the fresh/morphine-naive prepns. (pD2 6.72 ± 0.05, n = 8) than either the overnight-stored/morphine-naive (pD2 6.42 + 0.11, n = 8) or the overnight-stored/morphine exposed (pD2 6.44 ± 0.14, n = 8), there was no significant difference between the overnight models in their sensitivity to morphine. The latter observation indicates that overnight exposure of ileal segments to 10 μM morphine at 4° failed to induce tolerance to morphine. The μ **opiate** receptor antagonist, naloxone (10 μM), produced contractions in both fresh/morphine-naive and overnight-stored/morphine-naive ileal segments following acute exposure to 10 μM morphine. Naloxone (10 μM) also produced contractions in 2/9 fresh/morphine-naive, 1/9 overnight-stored/morphine-naive and 7/9 overnight-stored/morphine-exposed prepns. in the absence of morphine. The greater incidence of naloxone-induced contractions in overnight-stored/morphine-exposed prepns., suggests that dependence in this model is the product of adaptive changes that outlive the presence of morphine. The **selective** α2-adrenoceptor agonists, clonidine (0.3 μM) and 5-bromo-6-[2-imidazolin-2-ylamino]quinoxaline bitartrate (UK-14304, 1 μM), inhibited naloxone-induced contractions in overnight-stored/morphine-exposed prepns. of ileal segments, suggesting that the response is due to transmitter release from the myenteric plexus. The findings in the present study indicate that tolerance and dependence to morphine in ileal segments of the guinea pig can be functionally dissociated by overnight exposure to morphine at 4°. The development of tolerance to morphine, unlike dependence, appears to be a temperature-dependent process. This also raises the possibility that naloxone possesses intrinsic neg. agonism at morphine-sensitive receptors, which is manifested as a functional response only after adaptive changes in the myenteric plexus following exposure to morphine.

L12 ANSWER 23 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(intrinsic neg. agonism of, at morphine-sensitive receptors of myenteric plexus)

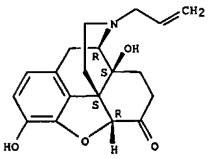
RN **465-65-6** CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 24 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 119:20393 CA
TITLE: Enhancement of the **opiate** withdrawal response by antipsychotic **drugs** in guinea pigs is not mediated by sigma binding sites
AUTHOR(S): Brent, Paul J.; Chahl, Loris A.
CORPORATE SOURCE: Fac. Med., Univ. Newcastle, Newcastle, 2308, Australia
SOURCE: European Neuropsychopharmacology (**1993**), 3(1), 23-32
CODEN: EURNE8; ISSN: 0924-977X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the σ ligands (+)- and (-)-SKF 10047 (1 and 10 mg/kg, s.c.), pentazocine (20 mg/kg, s.c.) and di-o-tolylguanidine (DTG) (1 and 10 mg/kg s.c.), the noncompetitive NMDA (N-methyl-D-aspartate) antagonists ketamine (20 mg/kg s.c.) and MK-801 (0.025, 0.1 and 1 mg/kg s.c.), atypical neuroleptic **drugs** with (remoxipride 25 mg/kg s.c.) and without (raclopride 10 mg/kg s.c.; clozapine 25 mg/kg s.c.) affinity for σ sites, and atropine sulfate (20 mg/kg s.c.) were investigated on the **opiate** withdrawal response induced by naloxone (15 mg/kg s.c.) in guinea pigs treated 2 h before with a single dose of morphine sulfate (15 mg/kg s.c.). (+)- And (-)-SKF 10047, pentazocine, ketamine and MK-801, given 0.5 h before naloxone, attenuated the increased locomotor activity and other behaviors associated with morphine withdrawal. The **selective** σ ligand DTG and remoxipride had no effect on the withdrawal response but reclopride, clozapine, and atropine exacerbated the response. It is concluded that exacerbation of the morphine withdrawal response by neuroleptics is not related to σ activity but to other mechanisms. Furthermore NMDA but not σ mechanisms might play a role in the morphine withdrawal response.
IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(morphine withdrawal induction by, neuroleptics enhancement of, σ-receptors mediation of)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

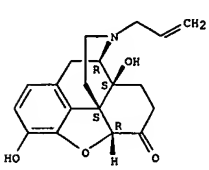
Absolute stereochemistry.



L12 ANSWER 24 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

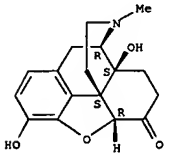
L12 ANSWER 25 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 116:248369 CA
TITLE: Manifestations of acute **opiate** withdrawal contracture in rabbit jejunum after μ-, κ- and δ-receptor agonist exposure
AUTHOR(S): Valeri, Pacifico; Morrone, Luigi A.; Romanelli, Luca
CORPORATE SOURCE: Inst. Pharmacol. Pharmacogn., Univ. Rome 'La Sapienza', Rome, 00185, Italy
SOURCE: British Journal of Pharmacology (**1992**), 106(1), 39-44
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following a 5 min in vitro exposure to morphine (1.3 + 10-7M), U-50,488H (2.5 + 10-8M) and deltorphin (1.6 + 10-8-6.5 + 10-9M), the rabbit isolated jejunum exhibited a precipitated contracture after the addition of naloxone (2.75 + 10-7M). The precipitated responses to U-50,488H and deltorphin but not to morphine were reproducible in the same tissue. The precipitated contractures were blocked completely by tetrodotoxin (3 + 10-7M), partially by atropine (1.5 + 10-7M) and not affected by hexamethonium (1.4 + 10-5M). Naloxone administration (2.75 + 10-7M) before the agonist prevented the development of the adaptive response to morphine and U-50,488H but not to deltorphin. The **selective** antagonists norbinaltorphimine (2.7 + 10-8-2.7 + 10-9M) and naltrindole (1.1 + 10-7M) prevented the adaptive response development only to the resp. agonists. The opioid agonists partially inhibited the spontaneous activity of the tissue. This study has shown that independent activation of μ-, κ- and δ-opioid receptors can induce dependence in this isolated tissue. Rabbit jejunum is a suitable tissue for studying the acute effects of opioids on the adaptive processes determined by their administration.
IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(**opiate** withdrawal contracture in jejunum induced by, after μ-, κ- and δ-receptor agonist exposure)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 26 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 116:189202 CA
TITLE: Forensic **drug** testing for opiates. IV. Analytical sensitivity, specificity, and accuracy of commercial urine **opiate** immunoassays
AUTHOR(S): Cone, Edward J.; Dickerson, Sandra; Paul, Buddha D.; Mitchell, John M.
CORPORATE SOURCE: Addict. Res. Cent., Natl. Inst. Drug Abuse, Baltimore, MD, 21224, USA
SOURCE: Journal of Analytical Toxicology (**1992**), 16(2), 72-8
CODEN: JATOD3; ISSN: 0146-4760
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four com. immunoassays, TDx Opiates (TDx), Coast-A-Count Morphine in Urine (CAC), Abuscreen RIA for Morphine (ABUS), and Emit d.a.u. **Opiate** Assay (EMIT), were tested for sensitivity, specificity, and accuracy with urine specimens containing known amts. of opiates and **opiate** metabolites. The immunoassays were evaluated in a semiquant. mode by comparison of morphine equivalent to GC/mass spectrometry (MS) assay of free and total morphine and codeine or to target concns. In all cases, the apparent sensitivities of the assays were higher than those required for detection of morphine at cutoffs mandated by the Health and Human Services guidelines for testing of Federal workers. The apparent specificities of the immunoassays varied considerably. The CAC assay was highly **selective** for free morphine, whereas TDx, ABUS, and EMIT demonstrated broad cross-reactivity with other opiates. Comparison of semiquant. results from the immunoassays with GC/MS data indicated a high degree of accuracy for determination of morphine levels. Generally, the patterns of sensitivity and cross-reactivity were unique for each assay, indicating that a detailed knowledge of assay performance characteristics is necessary for accurate interpretation of forensic urine testing data.
IT **76-41-5**, Oxymorphone
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in human urine by com. immunoassay)
RN 76-41-5 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, (5α)- (9CI) (CA INDEX NAME)

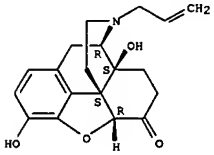
Absolute stereochemistry.



L12 ANSWER 26 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

L12 ANSWER 27 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 115:270548 CA
TITLE: Effects of 5-HT3 receptor antagonists on behavioral measures of naloxone-precipitated opioid withdrawal
AUTHOR(S): Higgins, Guy A.; Nguyen, Peter; Joharchi, Narges; Sellers, Edward M.
CORPORATE SOURCE: Clin. Psychopharmacol. Program, Addict. Res. Found., Toronto, ON, M5S 2S1, Can.
SOURCE: Psychopharmacology (Berlin, Germany) (1991), 105(3), 322-8
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of the **selective** 5-HT3 receptor antagonists, ondansetron and MDL 72222, against various behaviors elicited by naloxone-precipitated morphine withdrawal were examined Rats made dependent upon morphine by the s.c. implantation of a 75 mg pellet, when challenged with naloxone (0.5 mg/kg, S.C.), 3 or 4 days later exhibited a wide range of behaviors including wet dog shakes, paw shakes, salivation and a marked weight loss. Pre-treatment with ondansetron (0.01-1 mg/kg, S.C.) or MDL 72222 (1-3 mg/kg, S.C.) failed to affect the incidence of these responses except weight loss, which was attenuated by both treatments. At doses similar to and below those required to elicit the withdrawal syndrome, naloxone produced a single-trial place aversion in morphine dependent rats. The place aversion produced by naloxone (0.05 mg/kg, S.C.) was antagonized by pre-treatment of ondansetron (0.1-1 mg/kg, S.C.) and MDL 72222 (1 mg/kg, S.C.) prior to conditioning. Chlordiazepoxide (10 mg/kg, I.P.) but not gepirone (3-10 mg/kg, S.C.) was similarly effective. It is concluded that 5-HT3 antagonists may attenuate some but not all behavioral signs associated with morphine withdrawal. Reasons for this apparent selectivity are discussed.
IT 465-65-6, Naloxone
RL: BIOL (Biological study)
(**opiate** withdrawal induced by, serotoninergic S3 antagonists effect on)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



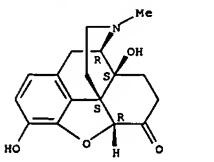
L12 ANSWER 27 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

L12 ANSWER 28 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 115:127034 CA
TITLE: Composition and method for **selective** enhancement of **opiate** activity and reduction of **opiate** tolerance and dependence
INVENTOR(S): Porreca, Frank
PATENT ASSIGNEE(S): Arizona Technology Development Corp., USA
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 415693	A1	19910306	EP 1990-309368	19900828
<-- R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 03163030	A2	19910715	JP 1990-226423	19900828
<--				
PRIORITY APPLN. INFO.:			US 1989-399590 A	19890828

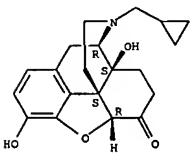
AB Disclosed is a composition for selectively enhancing **opiate** activity, including analgesic, antitussive, and sedative activity, as well as **opiate** activity in the treatment of dyspnea and modulation of intestinal motility, while reducing tolerance and dependence associated with chronic use of **opiate** analgesics. More specifically, a composition and method which selectively enhances **opiate** analgesia induced at μ receptors by direct or indirect action at the δ receptor sites of the central nervous system.
IT 76-41-5
RL: BIOL (Biological study)
(analgesic containing δ-receptor agonist and)
RN 76-41-5 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 29 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 115:119974 CA
TITLE: Biodegradable polymeric prodrugs of naltrexone .
AUTHOR(S): Bennett, D. B.; Li, X.; Adams, N. W.; Kim, S. W.; Hoes, C. J. T.; Feijen, J.
CORPORATE SOURCE: Dep. Pharm., Univ. Utah, Salt Lake City, UT, USA
SOURCE: Journal of Controlled Release (1991), 16(1-2), 43-52
CODEN: JCREEC; ISSN: 0168-3659
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The development of a biodegradable polymeric **drug** delivery system for the narcotic antagonist naltrexone may improve patient compliance in the treatment of **opiate** addiction. Random copolymers consisting of the α-amino acids, N5-(3-hydroxypropyl)-L-glutamine and L-leucine were synthesized with equimolar initial monomer feeds. The mol. weight of this chemical carrier was determined by viscometry and wide-angle light scattering. In order to get **selective** covalent coupling of **drug** to polymer, the 3-acetate and the 14-acetate derivative of naltrexone were synthesized and characterized by NMR. Hydrolytic conversion of each monoacetate to parent **drug** was monitored by HPLC and the rate constant was determined Both derivs. were coupled via hydrolytically labile carbonate linkages to the polymer hydroxyl groups. The **drug** conjugates were prepared as particles of various size ranges between 20 and 350 μ. In vitro studies in phosphate-buffered saline (pH 7.4) demonstrated a release rate dependence on particle size. Nearly constant plasma levels of naltrexone were obtained for one month after s.c. injection in rats.
IT **16590-41-3**, Naltrexone
RL: BIOL (Biological study)
(prodrugs for, biodegradable polymeric conjugates as, preparation and hydrolysis of)
RN 16590-41-3 CA
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α)- (9CI) (CA INDEX NAME)

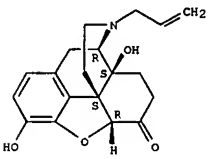
Absolute stereochemistry.



L12 ANSWER 30 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 113:126793 CA
TITLE: Affinity of **drugs** and peptides for U-69, 593-sensitive and -insensitive kappa **opiate** binding sites: the U-69,593-insensitive site appears to be the beta endorphin-specific epsilon receptor
AUTHOR(S): Nock, Bruce; Giordano, Anthony L.; Cicero, Theordore J.; O'Connor, Lynn H.
CORPORATE SOURCE: Sch. Med., Washington Univ., St. Louis, MO, 63110, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1990), 254(2), 412-19
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In vitro competition studies with rat brain were performed to systematically define the characteristics of the [3H]U 69,593 binding site and of the site selectively labeled by [3H]ethylketocyclazocine ([3H]EKC) (in the presence of U 69,593 and μ- and δ-blocking agents). The [3H]U 69,593 site has a binding selectivity profile that corresponds to that of the κ- **opiate** receptor. I.e., all κ compds., regardless of chemical class, and dynorphin A, the putative endogenous ligand for κ-receptors, bind to the site with high affinities, whereas μ and δ ligands and nonopiate compds. do not. The agonists U 69,593, ICI 197,067, and U 50,488 and antagonist nor-binaltorphimine have a useful degree of selectivity for the site. The [3H]EKC site has **opiate** receptor characteristics and appears to be the most abundant **opiate** receptor in rat brain, but its binding selectivity profile is not that of a κ-receptor. Instead, this non-μ, non-δ, non-κ site has the **pharmacol.** properties that correspond to those of the β-endorphin-specific, ε-receptor that has been hypothesized to exist for some time. No compound that is **selective** for the putative ε-site has yet been identified. Of the more than 50 compds. tested, all were either equally potent at the [3H]U 69,593 and [3H]EKC sites or were more potent at the [3H]U 69,593 site.
IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(ethylketocyclazocine and U 69,593 binding by brain receptors inhibition by)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

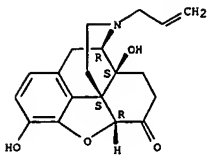
L12 ANSWER 30 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 31 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 113:126274 CA
TITLE: Naloxone potentiates contractile responses to epinephrine in isolated canine arteries
AUTHOR(S): Caffrey, J. L.; Hathorne, L. F.; Carter, G. C.; Sinclair, R. J.
CORPORATE SOURCE: Dep. Physiol., Texas Coll. Osteopath. Med., Fort Worth, TX, 76107, USA
SOURCE: Circulatory Shock (1990), 31(3), 317-32
CODEN: CRSHAG; ISSN: 0092-6213
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The beneficial pressor effects of naloxone in shock have been associated with existing adrenergic systems and in particular with circulating epinephrine. Vascular interactions among α adrenergic receptor agents, naloxone, and selected opioids were investigated in dogs. The addition of **pharmacol.** concns. of the **opiate** antagonist naloxone enhanced contractile responses to lower doses of epinephrine by >100% in isolated renal interlobar arteries. Naloxone lowered the EC50 for both epinephrine and norepinephrine but the magnitude of enhanced responses were much greater for epinephrine. Responses in the presence of naloxone to more **selective** α agonists, phenylephrine and clonidine, were also much less. The enhanced contraction cannot be demonstrated in the absence of added catecholamine and is eliminated by α- but not by β-adrenergic blockade. Dose responses for naloxone provided an EC50 (micromolar) above those reported for known **opiate** receptors. Representative μ (morphiceptin), δ (DADL), and κ (dynorphin 1-9) receptor agonists were ineffective in altering the EC50 for naloxone. Responses opposite to naloxone could be generated with **pharmacol.** addns. of another κ opioid, dynorphin 1-8. This effect was also accomplished without shifting the EC50 for naloxone to the right, suggesting dynorphin and naloxone operate via sep. mechanisms. The (+) stereoisomer of naloxone was as or more effective than (-) naloxone, adding support for a nontraditional or nonopiate receptor mechanism. Corticosterone produced responses indistinguishable from naloxone. These **pharmacol.** steroid-like responses to naloxone are used to suggest a hypothesis based upon modulation of extra-neuronal uptake and/or adrenergic receptor desensitization mechanisms.
IT **465-65-6**, (-)-Naloxone
RL: BIOL (Biological study)
(epinephrine-induced artery contraction potentiation by)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 31 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 32 OF 66 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 112:48610 CA

TITLE: **Pharmacological** actions of a novel mixed **opiate** agonist/antagonist: naloxone benzoylhydrazone

AUTHOR(S): Gistrak, Michael A.; Paul, Dennis; Hahn, Elliot F.; Pasternak, Gavril W.

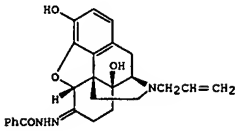
CORPORATE SOURCE: Cotzias Lab. Neuro-Oncol., Mem. Sloan Kettering Cancer Cent., New York, NY, 10021, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1989), 251(2), 469-76
CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB Naloxone benzoylhydrazone (I) is a novel **opiate** with potent actions at both μ- and κ-receptors. Analgesic studies in mice examining increasing doses of I with a fixed dose of morphine revealed a biphasic curve. I at doses as low as 1 μg/kg partially antagonized morphine analgesia. Higher I doses continued to inhibit the morphine analgesia in a dose-dependent manner, with the 1-mg/kg dose antagonizing it completely. As the I dose increased beyond 1 mg/kg, analgesia returned. I also produced a similar analgesic response when administered alone in mice and also was active in rats. I had excellent peroral activity, with an analgesic potency in mice equivalent to s.c. administration.

Naloxone reversed I analgesia far less effectively than it did morphine analgesia. Win44,441 antagonized both morphine and I analgesia with a similar potency, consistent with a κ-mechanism for I analgesia. Repeated administration of I resulted in tolerance. There was no analgesic cross-tolerance between I and either morphine or the κ1-**selective** agent U50,488H, implying a **selective** κ3 mechanism of analgesia. In addition to blocking morphine analgesia, low doses of I also partially reversed the inhibition of gastrointestinal transit in mice produced by morphine, antagonized completely morphine lethality, and precipitated withdrawal in morphine-dependent mice, confirming its antagonist activity at μ-receptors. The duration of I κ- and μ-actions differed dramatically. In mice, the analgesia typically lasted <2 h whereas the same I dose antagonized completely morphine analgesia, a μ action, for 16 h. The full sensitivity to morphine did

L12 ANSWER 32 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

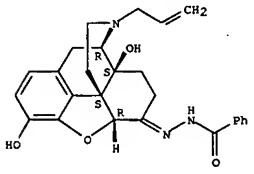
not return for 32 h. Thus, I is a potent long-lasting antagonist and orally active κ3 analgesic which should be valuable in studies on **opiate** analgesic mechanisms.

IT **119630-94-3**, Naloxone benzoylhydrazone
RL: BIOL (Biological study)
(analgesic and narcotic antagonist activity of, opioid receptor subtypes in mechanism of)

RN 119630-94-3 CA

CN Benzoic acid, [(5α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-ylidene]hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L12 ANSWER 33 OF 66 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 111:187449 CA

TITLE: **Pharmacological** manipulations of sucrose consumption in the Syrian hamster

AUTHOR(S): Cooper, Steven J.

CORPORATE SOURCE: Sch. Psychol., Univ. Birmingham, Birmingham, B15 2TT, UK

SOURCE: Pharmacology, Biochemistry and Behavior (1989), 33(3), 721-4
CODEN: PBBHAU; ISSN: 0091-3057

DOCUMENT TYPE: Journal

LANGUAGE: English

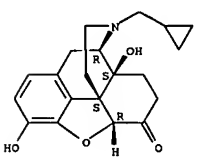
AB Nondeprived male Syrian hamsters (Mesocricetus auratus) were adapted to a daily schedule of 2-h access to a 10% sucrose solution The benzodiazepines midazolam (1.0-10 mg/kg) and flurazepam (1.0-10 mg/kg) produced dose-dependent increases in sucrose consumption. The α2-adrenergic agonist clonidine (0.01-0.3 mg/kg) had no effect on sucrose intake. Neither d-fenfluramine nor d-amphetamine affected sucrose ingestion, except at a large dose (10 mg/kg). Dose-dependent redns. in sucrose consumption were caused by the **opiate** antagonists naltrexone and nalmefene or the **selective** dopamine D2 receptor agonists N-0437 and quinpirole.

IT **16590-41-3**, Naltrexone
RL: BIOL (Biological study)
(sucrose consumption response to)

RN 16590-41-3 CA

CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 34 OF 66 CA COPYRIGHT 2005 ACS on STN

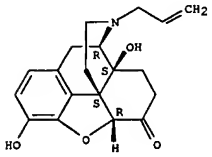
ACCESSION NUMBER: 111:126647 CA
TITLE: Enigmatic action of cyclosporin A on the naloxone-precipitated morphine withdrawal syndrome in mice
AUTHOR(S): Berthold, H.; Borel, J. F.; Flueckiger, E.
CORPORATE SOURCE: Preclin. Res., Sandoz Ltd., Basel, CH-4002, Switz.
SOURCE: Neuroscience (Oxford, United Kingdom) (1989), 31(1), 97-103
CODEN: NRSCDN; ISSN: 0306-4522
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Various alterations of the immune system attenuate the severity of morphine withdrawal. The effect of the immunosuppressive agent cyclosporin A on the naloxone-induced morphine withdrawal syndrome in the chronically dependent mouse was investigated. Cyclosporine suppressed stereotyped behavior such as jumping and forepaw treading, while wet shakes were potentiated. Withdrawal diarrhea was diminished as a consequence of a promotive action of cyclosporine on the intestine. The O-acetyl cyclosporine derivative, which is devoid of immunosuppressive activity, had no influence on withdrawal signs. The attenuating effect of cyclosporine was observed at a dose of 20 mg/kg i.p., which is not immunosuppressive in the mouse. It was also effective in animals lacking an intact immune system as a result of a genetic T-cell defect (nude mouse) or after **selective** ablation by whole-body irradiation Nude mice and irradiated normal mice developed dependence on morphine to the same extent as normal animals. Thus, an intact immune system is not a necessary prerequisite for cyclosporine to attenuate morphine withdrawal, and its action may be attributable to mechanisms other than immunosuppression. It is possibly a result of a direct effect of cyclosporine on the central nervous system structures involved in the behavioral expression of the **opiate** withdrawal syndrome.

IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(morphine withdrawal induction by, cyclosporine inhibition of symptoms of, immunity role in)

RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 34 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

L12 ANSWER 35 OF 66 CA COPYRIGHT 2005 ACS on STN

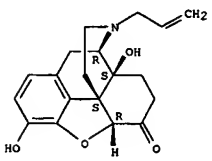
ACCESSION NUMBER: 111:108919 CA
TITLE: **Opiate** antagonists and self-stimulation: extinction-like response patterns suggest **selective** reward deficit
AUTHOR(S): Trujillo, Keith A.; Belluzzi, James D.; Stein, Larry
CORPORATE SOURCE: Coll. Med., Univ. California, Irvine, CA, 92717, USA
SOURCE: Brain Research (1989), 492(1-2), 15-28
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The response decrement patterns produced by **opiate** antagonists on intracranial self-stimulation behavior were studied in rats to determine if these **drugs** affect the reinforcement value of the stimulation or interfere with the ability of the animal to respond. Male rats pressed levers in 60-min sessions on a continuous reinforcement schedule for self-stimulation of the nucleus accumbens. Naloxone (2.0 and 20 mg/kg) and naltrexone (2.0 and 20 mg/kg) suppressed the self-stimulation only after a significant delay in an extinction-like response decrement pattern mimicking the effects of redns. in current intensity (75% and 50% of baseline). The increasing behavioral effects characteristic of the extinction pattern were observed despite the fact that testing began after the time point at which maximal suppression of self-stimulation occurs with these **drugs**, and when brain concns. of these **drugs** were declining. Since normal responding was observed for several minutes after the beginning of the session, the results may explain why long sessions are necessary to observe suppression of self-stimulation by **opiate** antagonists. The extinction-like pattern produced by these **drugs** suggests that **opiate** antagonists suppress self-stimulation by reducing the reinforcement value of the stimulation, rather than by interfering with the ability of animal to respond. These findings are consistent with a role for endogenous opioid peptides in brain self-stimulation reward.

IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(brain self-stimulation response to, extinction-like response in, endogenous opioids in)

RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

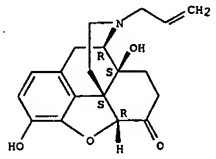
Absolute stereochemistry.



L12 ANSWER 35 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

L12 ANSWER 36 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 111:70797 CA
TITLE: Evidence that the aversive effects of opioid antagonists and κ-agonists are centrally mediated
AUTHOR(S): Bals-Kubik, R.; Herz, A.; Shippenberg, T. S.
CORPORATE SOURCE: Dep. Neuropharmacol., Max Planck Inst. Psychiatry, Planegg-Martinsried, D-8033, Fed. Rep. Ger.
SOURCE: Psychopharmacology (Berlin, Germany) (1989), 98(2), 203-6
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of central vs. peripheral opioid receptors in mediating the aversive effects of opioids was examined by use of an unbiased place preference conditioning procedure in rats. The non-**selective** opioid antagonist naloxone (NLX) produced conditioned aversion for the **drug**-associated place after s.c. as well as intracerebroventricular (i.c.v.) administration. Place aversions were also observed in response to the i.c.v. administration of the **selective** μ-antagonist CTOP. The **selective** δ-antagonist ICI 174,864 and the **selective** κ-antagonist norbinaltorphimine (nor-BNI) given i.c.v. were without effect. Place aversions were also produced by central applications of the **selective** κ-agonist U50,488 H and the dynorphin derivative E-2078. For those opioid ligands tested, the doses required to produce place versions were substantially lower following i.c.v. as compared to s.c. administration. The data confirm the κ-agonists and opioid antagonists produce aversive states in the **drug**-naive animal and demonstrate that this effect is centrally mediated. The ability of NLX and CTOP, in contrast to ICI 174,864 and nor-BNI, to produce place aversions suggests that the aversive effects of opioid antagonists result from the blockade of μ-receptors.
IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(behavioral place avoidance conditioned by, central opioid receptors in)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

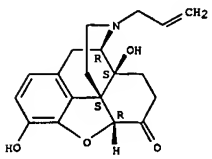
Absolute stereochemistry.



L12 ANSWER 36 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

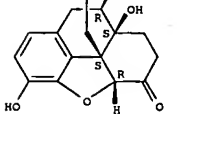
L12 ANSWER 37 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 109:85738 CA
TITLE: Interaction of enantiomeric pairs of opiates with phencyclidine binding sites in rat brain: identification of (+)-pentazocine as a ligand potentially suitable for imaging sigma binding sites using positron emission tomography
AUTHOR(S): Rothman, Richard B.; Bykov, Victor; Newman, Amy Hauck; Jacobson, A. E.; Rice, Kenner C.
CORPORATE SOURCE: Lab. Clin. Sci., NIMH, Bethesda, MD, 20892, USA
SOURCE: Neuropeptides (Edinburgh, United Kingdom) (1988), 12(1), 1-5
CODEN: NRPPDD; ISSN: 0143-4179
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Some unnatural opiates, which do not interact with classical **opiate** receptors, interact with phencyclidine (PCP) receptors. **Drugs** which bind to the PCP receptor antagonize the actions of glutamic acid mediated via the N-methyl-D-aspartate excitatory amino acid receptor, leading to their potential use as anti-ischemic and anticonvulsant agents. A PCP receptor antagonist has not yet been reported and chemical modification of unnatural opiates as a means to produce PCP antagonists or agonists with properties different than PCP has not been fully explored. The equilibrium dissociation consts. of 22 **opiate** compds. including 8 enantiomeric pairs for the rat brain PCP receptor were determined Pentazocine racemate bound weakly to the PCP sites but strongly to the haloperidol-sensitive σ-sites. This property may render pentazocine and its derivs. suitable for **selective** studies on σ-receptors in the presence of PCP receptors.
IT **465-65-6**, (-)-Naloxone
RL: BIOL (Biological study)
(phencyclidine receptor of brain binding of, equilibrium dissociation constant of)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



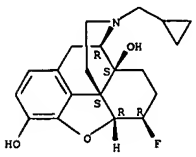
L12 ANSWER 38 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 108:52096 CA
TITLE: **Opiate** involvement in contrast media-induced blood pressure changes
AUTHOR(S): Harnish, Phillip P.; Mukherji, Monica; Northington, Frances K.; Kido, Daniel K.
CORPORATE SOURCE: Med. Cent., Univ. Rochester, Rochester, NY, USA
SOURCE: Investigative Radiology (1987), 22(11), 905-7
CODEN: INVRAV; ISSN: 0020-9996
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The i.v. administration of contrast media (CM) often alters blood pressure (BP). Osmolality plays a role, but the magnitude and even direction of change varies under similar (osmotic) conditions, indicating the involvement of other mechanisms. Male Wistar rats, anesthetized with pentobarbital, received meglumine diatrizoate, iohexol, or normal saline, 4 mL/kg, via a tail vein, while blood pressure was recorded continuously. Addnl. groups were pretreated with the **opiate** antagonist, naloxone (1 mg/kg, i.v.) or with an equal volume of normal saline 5 min prior to the diatrizoate injection. Diatrizoate caused an increase in BP relative to the saline control group; iohexol did not. Neither the saline nor naloxone pretreatment altered BP. Saline pretreatment did not alter the increase in BP produced by the diatrizoate. However, the diatrizoate-induced increase in BP was prevented by the naloxone pretreatment and was less than after the saline pretreatment. Release of endogenous opioids may play a role in BP changes caused by i.v. CM and CM-induced changes may be prevented **pharmacol.** with the **selective opiate** blocker, naloxone.
IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(contrast media-induced blood pressure changes inhibition by)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 39 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 107:229065 CA
TITLE: Chronic morphine upregulates a μ- **opiate** binding site labeled by [3H]cycloFOXY: a novel **opiate** antagonist suitable for positron emission tomography
AUTHOR(S): Rothman, Richard B.; McLean, S.; Bykov, V.; Lessor, R.
A.; Jacobson, A. E.; Rice, K. C.; Holaday, J. W.
CORPORATE SOURCE: Lab. Preclin. Pharmacol., St. Elizabeths Hosp., Washington, DC, 20032, USA
SOURCE: European Journal of Pharmacology (1987), 142(1), 73-81
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CycloFOXY (17-cyclopropylmethyl-3,14-dihydroxy-4,5-α-epoxy-6-β-fluoromorphinan) is a novel **opiate** antagonist synthesized as a ligand suitable for in vivo visualization of **opiate** receptors using positron emission transaxial tomog. [3H]cycloFOXY labels two distinct **opiate** binding sites in rat brain membranes, tentatively identified as μ and κ. Furthermore, chronic administration of morphine results in a **selective** up-regulation of the μ binding site. The implications of this finding for models of the opioid receptors are discussed.
IT 103223-57-0
RL: BIOL (Biological study)
(μ- **opiate** receptors of brain labeling by, morphine tolerance effect on, positron emission tomog. for determination of)
RN 103223-57-0 CA
CN Morphinan-3,14-diol, 17-(cyclopropylmethyl)-4,5-epoxy-6-fluoro-, (5α,6β)- (9CI) (CA INDEX NAME)

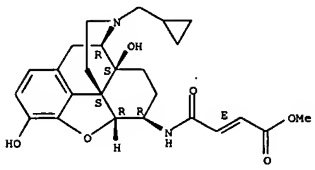
Absolute stereochemistry.



L12 ANSWER 40 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 107:190810 CA
TITLE: Kappa opioids in rhesus monkeys. II. Analysis of the
antagonistic actions of quadazocine and β-funaltrexamine
AUTHOR(S): Dykstra, Linda A.; Gmerek, Debra E.; Winger, Gail; Woods, James H.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1987), 242(2), 421-7
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rhesus monkeys, kappa opioid agonists have been shown to 1) increase urinary output, 2) increase tail-withdrawal latencies from warm water and 3) produce distinct discriminative stimulus effects. In order to explore further the relation between these effects and activity at the kappa opioid receptor type, the antagonist activity of quadazocine against several kappa opioid agonists was examined with the tail-withdrawal and **drug**-discrimination procedures. Quadazocine dose dependently antagonized the increases in tail-withdrawal latency produced by the kappa
agonists bremazocine, ethylketazocineand U-50,488, as well as the discriminative stimulus effects of these **drugs**. The dose-ratio anal. of Schild revealed apparent pA2 values for quadazocine in combination with bremazocine, ethylketazocine and U-50,488 of 6.1, 6.4 and
6.4, resp., with the tail-withdrawal procedure and 6.3, 6.4 and 6.1, resp., with the **drug**-discrimination procedure. Quadazocine also antagonized the effects of a mu agonist (morphine) in the tail-withdrawal procedure, and the apparent pA2 value for these data was 8.2. The activity of the mu-**selective** alkylating agent, β-funaltrexamine (β-FNA), was examined alone and in combination with the kappa agonist ethylketazocine in the urinary-output, tail-withdrawal and **drug**-discrimination procedures. At about 30 to 60 min postinjection, β-FNA alone produced ethylketazocine-appropriate responding under the **drug**-discrimination procedure and increased urine output but did not increase tail-withdrawal latencies.
At 24 to 48 h postinjection, β-FNA did not antagonize effects of ethylketazocine in any of the 3 procedures. Under the same conditions of administration, β-DNA did, however, antagonize the effects of mu agonists in the tail-withdrawal procedure and in the **drug**-discrimination procedure.
IT 72782-05-9, β-Funaltrexamine
RL: BIOL (Biological study)
(**opiate pharmacol.** antagonism by, receptor mediation of)
RN 72782-05-9 CA
CN 2-Butenoic acid, 4-[[(5α,6β)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]amino]-4-oxo-, methyl ester, (2E)- (9CI) (CA
INDEX NAME)

Absolute stereochemistry.

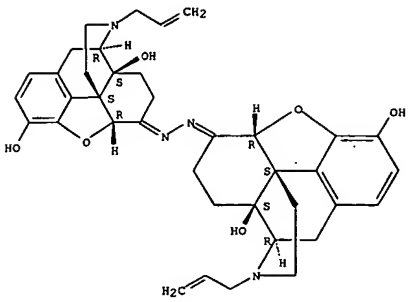
L12 ANSWER 40 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
Double bond geometry as shown.



L12 ANSWER 41 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 107:169055 CA
TITLE: H-D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH2: a potent and **selective** antagonist for mu opioid receptors
AUTHOR(S): Gulya, K.; Lui, G. K.; Pelton, J. T.; Kazmierski, W.; Hruby, V. J.; Yamamura, H. I.
CORPORATE SOURCE: Dep. Pharmacol. Chem., Univ. Arizona, Tucson, AZ, 85724, USA
SOURCE: NIDA Research Monograph (1986), 75(Prog. Opioid Res.), 209-12
CODEN: MIDAD4; ISSN: 0361-8595
DOCUMENT TYPE: Journal
LANGUAGE: English
AB H-D-Phe-cyclo(Cys-Tyr-D-Trp-Orn-Thr-penicillamine)-Thr-NH2(CTOP) exhibited
high affinity [50% inhibitory concentration(IC50)= 2.80 nM] in displacing [3H]naloxone binding and showed an exceptional selectivity for μ receptors with a 50% IC ([D-penicillamine]enkephalin)/IC50 (naloxone) ratio of 4840, whereas it displayed very low affinity for somatostatin receptors (IC50 = 22,700 nM) in rat brain binding assays. [3H]CTOP was evaluated for its in vitro binding properties towards the μ receptors in rat brain membrane prepns. Association and dissociation of [3H]CTOP binding to
μ opioid receptors were rapid at 25° with a kinetic dissociation value of 0.6m nM. Saturation expts. gave an apparent dissociation constant value of
1.11 nM and a maximum binding capacity of 136 fmol/mg protein at 25°. Specific [3H]CTOP binding was inhibited by a number of different opioid and
opiate ligands. Among them, putative μ receptor-specific ligands, such as naloxone, naltrexone, and CTOP inhibited the binding with
high affinity, whereas δ receptor-specific compds. or nonopioid **drugs** inhibited specific [3H]CTOP binding with low affinity or they were ineffective.
IT 82824-01-9, Naloxonazine
RL: PROC (Process)
(binding of, by μ-receptors)
RN 82824-01-9 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, [(5α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-ylidene]hydrazone, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

L12 ANSWER 41 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 42 OF 66 CA COPYRIGHT 2005 ACS on STN

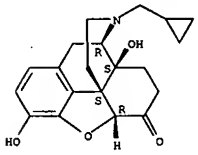
ACCESSION NUMBER: 106:149365 CA
TITLE: Differential effects of CGS 8216 and naltrexone on ingestional behavior
AUTHOR(S): Kirkham, T. C.; Barber, D. J.; Heath, R. W.; Cooper, S. J.
CORPORATE SOURCE: Dep. Psychol., Univ. Birmingham, Birmingham, B15 2TT, UK
SOURCE: Pharmacology, Biochemistry and Behavior (1987), 26(1), 145-51
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the pyrazoloquinoline CGS 8216 (I) [77779-60-3] (a partial benzodiazepine receptor inverse agonist) and the **opiate** antagonist naltrexone [16590-41-3], were compared in several tests of ingestion in non-deprived and deprived male rats. Both naltrexone (0.1-10.0 mg/kg, s.c.) and I (1.25-10.0 mg/kg, i.p.) reduced the consumption of a highly palatable saccharin-glucose solution by nondeprived rats. Both compds. were also effective in reducing, dose-dependently, the intake of palatable sweet or oily mash by non-deprived animals. Hence, naltrexone and I attenuated palatability-induced ingestional responses, and sweet taste was not necessary for this effect to occur. The 2 **drugs** also reduced the intake of the saccharin-glucose solution in food-deprived rats, but their effects diverged in water-deprived animals. I had relatively little effect in the thirsty animals, whereas the effect of naltrexone was enhanced. This difference was underscored in a final test of deprivation-induced consumption of water. Naltrexone reduced the drinking, but I had no effect. Taken together, these data indicate that I was more **selective** in its effects on ingestion.

IT **16590-41-3**, Naltrexone
RL: BIOL (Biological study)
(ingestional behavior differential response to)

RN 16590-41-3 CA
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 42 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

L12 ANSWER 43 OF 66 CA COPYRIGHT 2005 ACS on STN

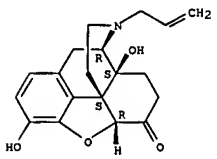
ACCESSION NUMBER: 106:78602 CA
TITLE: **Selective** regional effect of various neuroactive **drugs** on bromocriptine concentration in the brain of rats
AUTHOR(S): Rabey, J. M.; Graff, E.; Oberman, Z.; Flechter, S.; Vardi, J.
CORPORATE SOURCE: Ichilov Hosp., Tel-Aviv, Univ., Tel Aviv-Jaffa, Israel
SOURCE: Acta Neurologica Scandinavica (1986), 74(4), 289-92
CODEN: ANRSAS; ISSN: 0001-6314
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In order to check the mechanism of the interaction of neuroactive **drugs** with bromocriptine [25614-03-3] in rats, different neuroactive **drugs** were administered together with bromocriptine. After a single i.p. injection, the bromocriptine concentration in the striatum was 13.1 ng/mg protein, and in the hypothalamus 13.9 ng/mg protein. The largest increase in the bromocriptine content in the striatum was found after the concomitant administration of naloxone [**465-65-6**], an **opiate** receptor blocker (21.2 ng/mg protein). The largest increase of the bromocriptine content in the hypothalamus was found after the concomitant injection of methysergide [361-37-5], a serotonin receptor blocker (27.8 ng/mg protein). Amantadine [768-94-5], diazepam [439-14-5] and haloperidol [52-86-8] caused the largest decrease in 2 regions. The mechanism of interaction and therapeutic implication of these findings are discussed.

IT **465-65-6**, Naloxone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bromocriptine **pharmacokinetics** in brain response to)

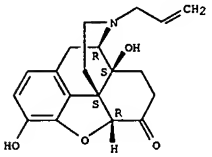
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



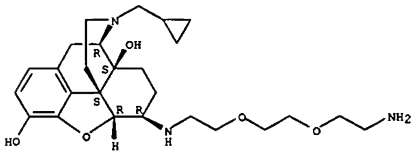
L12 ANSWER 44 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 106:534 CA
TITLE: **Pharmacology** of δ-opioid receptors in the hamster vas deferens
AUTHOR(S): Sheehan, Michael J.; Hayes, Ann G.; Tyers, Michael B.
CORPORATE SOURCE: Dep. Neuropharmacol., Glaxo Group Res. Ltd., Ware/Hertfordshire, SG12 0DJ, UK
SOURCE: European Journal of Pharmacology (1986), 130(1-2), 57-64
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Elec. evoked contractions of the hamster isolated vas deferens were inhibited only by opioid **drugs** which have agonist activity at δ-opioid receptors. Opioids which are μ-, κ- or σ-**selective** were either inactive or were antagonists. The compound β-funaltrexamine [72782-05-9], which irreversibly blocks μ- and δ-opioid receptors, caused a flattening of the concentration-response curve and a reduced maximum inhibition available to δ-opioid agonists. Anal. of the curves by the double-reciprocal null method enabled the affinity of these agonists at δ-opioid receptors to be calculated
IT **465-65-6**, Naloxone
RL: BIOL (Biological study)
(δ-opioid receptors of vas deferens response to, in hamster)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



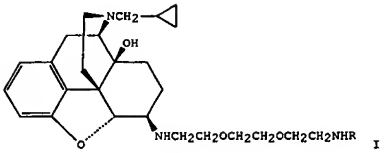
L12 ANSWER 45 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and opioid antagonist activity of)
RN 101858-62-2 CA
CN Morphinan-3,14-diol, 6-[[2-[2-(2-aminoethoxy)ethoxy]ethyl]amino]-17-(cyclopropylmethyl)-4,5-epoxy-, trihydrochloride, (5α,6β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



. ●3 HCl

L12 ANSWER 45 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 104:225074 CA
TITLE: Investigation of the structural requirements for the κ- **selective** opioid receptor antagonist 6β,6β'-[ethylenebis(oxyethyleneimino)]bis[17-(cyclopropylmethyl)-4,5α-epoxymorphinan-3,14-diol] (TENA)
AUTHOR(S): Botros, S.; Lipkowski, A. W.; Takemori, A. E.; Portoghese, P. S.
CORPORATE SOURCE: Coll. Pharm., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Journal of Medicinal Chemistry (1986), 29(5), 874-6
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 104:225074
GI



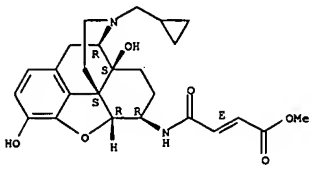
I

AB In an effort to determine whether or not the basic nitrogens in the spacer of the bivalent ligand 6β,6β'-[ethylenebis(oxyethyleneimino)]bis[17-(cyclopropylmethyl)-4,5α-epoxymorphian-3,14-diol (TENA) is responsible for its **selective** κ opioid antagonist activity, monovalent analogs I [R = H, C(:NH)NH2, PhCH2] were prepared from β-naltrexamine. I (R = H) behaved as a potent opioid agonist in the guinea pig ileum preparation (GPI) and possessed no significant κ opioid antagonist activity (IC50 ratio = 1) relative to TENA (IC50 ratio = 20). The agonist activity of I [R = C(:NH)NH2, PhCH2] interfered with the opioid antagonist assay and therefore did not permit evaluation of antagonist activity in a concentration range where TENA is effective. Although the results obtained with I (R=H) are consistent with the requirement of a second **opiate pharmacophore** (rather than a second basic nitrogen in the spacer) for the κ antagonist activity of TENA, the potent agonism associated with these monomers do not allow a firm conclusion in this regard.
IT **101858-62-2P**

L12 ANSWER 46 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 104:681 CA
TITLE: Effects of β-funaltrexamine in normal and morphine-dependent rhesus monkeys: observational studies
AUTHOR(S): Gmerek, Debra E.; Woods, James H.
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109-0010, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1985), 235(2), 296-301
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The behavioral effects of the opioid receptor alkylating agent β-funaltrexamine (β-FNA) [72782-05-9] were assessed in normal (**drug**-naive) and morphine [57-27-2]-dependent rhesus monkeys. In normal monkeys, β-FNA (10 mg/kg, s.c.) produced muscle relaxation and stupor, which could be reversed by the opioid antagonist Win 44,441. Given as a 48-h pretreatment, β-FNA antagonized the behavioral effects of acute morphine, but not those of 2 κ-agonists, ethylketazocine and Mr 2033 (UM 1072). In morphine-dependent monkeys, β-FNA [10 mg/kg, s.c. and 0.003 mg intracerebroventricularly (i.c.v.)] precipitated severe abstinence which lasted for 3 days. β-FNA was more than 13,000 times more potent in precipitating withdrawal after i.c.v. than after s.c. administration, whereas naltrexone and Win 44,441 were equipotent by these routes. Deprivation-induced abstinence (14 h) and withdrawal of similar severity precipitated by naltrexone, Win 44,441 or naloxonazine were suppressed completely by 17.5 mg/kg of morphine. In contrast, 320 mg/kg of morphine failed to suppress completely a withdrawal syndrome of the same severity elicited by s.c. or i.c.v. β-FNA. Thus, β-FNA has reversible opioid agonist and insurmountable μ **selective** antagonist activity in the rhesus monkey.
IT **72782-05-9**
RL: PRP (Properties)
(behavioral effects of, in morphine dependence, **opiate** agonist and antagonist activity in relation to)
RN 72782-05-9 CA
CN 2-Butenoic acid, 4-[[(5α,6β)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]amino]-4-oxo-, methyl ester, (2E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L12 ANSWER 46 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 47 OF 66 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 103:172000 CA

TITLE: A **selective** potentiation by naloxone of L-dopa but not atropine suppression of oxotremorine-induced tremor in mice

AUTHOR(S): Quock, Raymond M.; Lucas, T. Scott

CORPORATE SOURCE: Sch. Dent., Marquette Univ., Milwaukee, WI, 53233, USA

SOURCE: Journal of Pharmacy and Pharmacology (**1985**), 37(9), 673-4
CODEN: JPPMAB; ISSN: 0022-3573

DOCUMENT TYPE: Journal

LANGUAGE: English

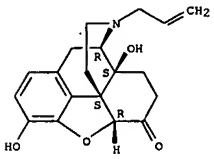
AB Oxotremorine [70-22-4] induced tremor activity in mice (a model of parkinsonism) was suppressed by treatment with either L-dopa [59-92-7] or atropine [51-55-8]; pretreatment with the **opiate** receptor blocker naloxone [**465-65-6**] potentiated the antitremor effect of L-dopa but not that of atropine. These findings indicate a **selectivity** of **drug** interaction between naloxone and L-dopa.

IT **465-65-6**
RL: BIOL (Biological study)
(atropine and dopa suppression of oxotremorine-induced tremor response to)

RN 465-65-6 CA

CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 48 OF 66 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 103:545 CA

TITLE: Characterization of a labile naloxone binding site (λ site) in rat brain

AUTHOR(S): Grevel, Joachim; Yu, Victor; Sadee, Wolfgang

CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, USA

SOURCE: Journal of Neurochemistry (**1985**), 44(5), 1647-56
CODEN: JONRA9; ISSN: 0022-3042

DOCUMENT TYPE: Journal

LANGUAGE: English

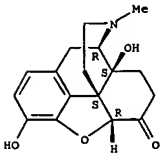
AB A high-affinity binding site **selective** for naloxone [**465-65-6**] and other 4,5-epoxymorphinans (λ site) has been described in rat brain. Following homogenization of freshly dissected brain, the λ sites convert from a high-affinity to a low-affinity state. When measured with [3H]naloxone, the decay is very rapid at 20° (t1/2 < 2 min), whereas it is progressively slowed at lower temps. Proteinase inhibitors, antioxidants, and sulfhydryl group-protecting agents failed to prevent this conversion. Kinetic measurements of μ and λ binding at varying temps. demonstrated that the decrease in λ binding does not coincide with the concurrent increase in μ binding and that the loss of high-affinity λ binding at 20° can be partially restored when the temperature is lowered to 0°. The low-affinity state of the λ site is rather stable in the Tris buffer homogenates and is susceptible to digestion by a protease. The (-)-isomer of WIN 44441 [71276-44-3], a benzomorphan **drug**, binds to λ sites with moderate affinity (dissociation constant, KD = 63 nM), whereas the (+)-isomer [77844-05-4] does not (KD > 10,000 nM), thus establishing stereoselectivity of the binding process. Neither the high-affinity nor the low-affinity state of λ binding is significantly affected by the presence of 100 mM NaCl or 50 μM Gpp(NH)p [34273-04-6], (a GTP analog), which is in contrast to the dramatic effect of these agents on the established opioid receptor system. Naltrexone [16590-41-3], naloxone [**465-65-6**], nalorphine, and morphine [57-27-2] (in this order of decreasing potency) bind to the λ site in vivo in intact rat brain over dosage ranges that are commonly employed in **pharmacol.** studies.

IT **76-41-5**
RL: BIOL (Biological study)
(λ-opioid receptor of brain binding by)

RN 76-41-5 CA

CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, (5α)- (9CI) (CA INDEX NAME)

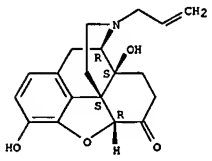
Absolute stereochemistry.



L12 ANSWER 48 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

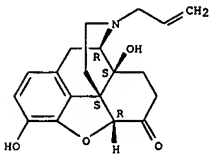
L12 ANSWER 49 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 102:179777 CA
TITLE: **Selective** attenuation of sweetened milk consumption by **opiate** receptor antagonists in male and female rats of the Roman strains
AUTHOR(S): Cooper, S. J.; Barber, D. J.; Barbour-McMullen, J.
CORPORATE SOURCE: Dep. Psychol., Univ. Birmingham, Birmingham, B15 2TT, UK
SOURCE: Neuropeptides (Edinburgh, United Kingdom) (1985), 5(4-6), 349-52
CODEN: NRPPDD; ISSN: 0143-4179
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Male and female rats of the 3 Roman strains (Roman High-, Roman Low-, and Roman Control Avoidance; RHA, RLA and RCA, resp.) were familiarized with a highly palatable sweetened milk in a daily 30-min test. The animals were never food or water deprived prior to the test. Daily milk intake stabilized at a high level before **drug** tests were initiated. Effects of naloxone [465-65-6], diprenorphine [14357-78-9], WIN 44,441-3 [71276-43-2], MR 2266 [56649-76-4], MR 2267 [56649-75-3], and ICI 154129 [83420-94-4] on milk consumption were investigated. Naloxone, diprenorphine, and MR 2266 each had comparable anorectic effects across strains and sexes. WIN 44,441-3 was relatively ineffective; MR 2267 and ICI 154129 were without effect on milk consumption.
IT **465-65-6**
RL: BIOL (Biological study)
(appetite response to, genetics in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

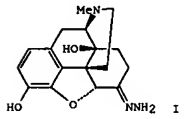


L12 ANSWER 50 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 102:143104 CA
TITLE: Actions of **opiate** antagonists in relation to behavioral processes
AUTHOR(S): Morse, W. H.; Goldberg, S. R.; Katz, J. L.
CORPORATE SOURCE: Harvard Med. Sch., Boston, MA, USA
SOURCE: Neurology and Neurobiology (1985), 13(Behav. Pharmacol.: Curr. Status), 149-66
CODEN: NEUND9; ISSN: 0736-4563
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Naloxone [465-65-6] >6 mg/kg were needed to decrease responding in rhesus monkeys to food presentations not dependent on morphine [57-27-2] and responding was disrupted non-selectively in both components of the schedule. After daily i.m. injections of morphine at doses as low as 1-3 mg/kg, cumulative intake of naloxone 100 times less decreased responding. Gradually, responding became selectively suppressed in the component associated with naloxone injections and few injections occurred.
Only when the total intake of naloxone was limited did **selective** suppression occur. When the naloxone injection dose was low and the maintenance dose of morphine was abruptly withheld, responding in the next session was not suppressed by cumulative naloxone doses ≤0.06 mg/kg. However, even after exposure to morphine had ceased, responding could be selectively suppressed by injection doses of naloxone >0.01 mg/kg. The effects of **opiate** antagonists on behavior in morphine-dependent subjects is discussed in relation to the **pharmacol.** effects of opiates and the withdrawal-like effects of **opiate** antagonists.
IT **465-65-6**
RL: BIOL (Biological study)
(behavior response to, morphine dependence in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 51 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 101:103930 CA
TITLE: Oxymorphazone: a long-acting **opiate** analgesic
AUTHOR(S): Ling, Geoffrey S. F.; Galetta, Steven; Pasternak, Gavril W.
CORPORATE SOURCE: Med. Coll., Cornell Univ., New York, NY, 10021, USA
SOURCE: Cellular and Molecular Neurobiology (1984), 4(1), 1-13
CODEN: CMNEDI; ISSN: 0272-4340
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

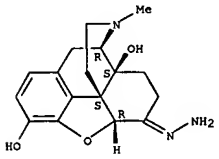


I

AB Addition of oxymorphazone (I) [73697-35-5] to rat brain homogenates caused a **selective** and long-acting inhibition of the high-affinity (μ1) binding of a number of [3H]opioids. This inhibition was not affected by extensive wash procedures which effectively reverse the effects of morphine and naloxone. A similar, persistent inhibition of binding was observed following in vivo administration of the **drug**. Both systemically and intracerebroventricularly, oxymorphazone produced dose-dependent analgesia. Acutely administered oxymorphazone (ED50, 0.6 mg/kg) was approx. half as potent as oxymorphone (ED50, 0.3 mg/kg), in the tail-flick assay; administered at their ED50 doses, both compds. had the same durations of action. As the doses of **drug** were increased, however, the time course of oxymorphazone's analgesia became far more prolonged than that of oxymorphone. Following the administration of oxymorphazone (100 mg/kg), >50% of the mice remained analgesic for >24 h, as opposed to none of the mice given oxymorphone (100 mg/kg). Oxymorphazone was far more potent intraventricularly (i.c.v.) than systemically. Fifty percent of the mice remained analgesic for >20 h following the injection of 40 μg/mouse (i.c.v.), whereas no mice remained analgesic after 20 h following doses of oxymorphone as high as 50 μg/mouse (i.c.v.). These long-lasting analgesic actions of oxymorphazone could not be easily explained on **pharmacokinetic** grounds. Repeated administration of oxymorphazone daily for 3 days resulted in significant tolerance.
IT **73697-35-5**
RL: BIOL (Biological study)
(analgesia from, **pharmacol.** of)
RN 73697-35-5 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, hydrazone, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

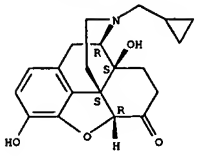
L12 ANSWER 51 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
Double bond geometry unknown.



L12 ANSWER 52 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 101:48607 CA
TITLE: Visualization of **opiate** receptor upregulation by light microscopy autoradiography
AUTHOR(S): Tempel, Ann; Gardner, Eliot L.; Zukin, R. Suzanne
CORPORATE SOURCE: Dep. Biochem., Albert Einstein Coll. Med., Bronx, NY, 10461, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1984**), 81(12), 3893-7
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Light-microscopy autoradiog. was used to visualize neuroanatomical patterns of brain **opiate**-receptor up-regulation in response to chronic naltrexone [16590-41-3] administration. Slide-mounted brain sections of frozen rat brain were labeled in vitro with dihydro[3H]morphine, a relatively **selective** μ-opioid ligand. The greatest relative increases in **opiate**-receptor d. were observed in the nucleus accumbens, the amygdala, striatal patches, nuclei of the thalamus and hypothalamus, layers I and III of neocortex, substantia nigra compacta, midbrain periaqueductal gray regions, and the parabrachial nuclei of the brainstem. The substantia nigra reticulata, surrounding areas of striatal patches, and the locus ceruleus, were not affected by this **drug** treatment. These findings demonstrate that chronically administered naltrexone differentially regulates **opiate** receptors throughout the brain. In particular, 3 brain systems appear to be target areas of receptor up-regulation: (i) the dopamine A9/A10 systems, (ii) the limbic system, and (iii) structures that receive input from afferent sensory pathways. Two possible mechanisms to account for this finding are (i) that the **drug** does not have uniform effects throughout the brain or (ii) that the receptors themselves may be associated with different functional systems. Receptor-d. changes are paralleled by increases in methionine-enkephalin [58569-55-4] content in the striatum, nucleus accumbens, periaqueductal gray, and hypothalamic areas of chronic naltrexone-treated rats. Thus **opiate** receptors and opioid peptides appear to be subject to regulatory mechanisms similar to those that modulate other neurotransmitters and their receptors. These results document in a visual manner brain patterns of **opiate**-ceptor up-regulation.
IT **16590-41-3**
RL: BIOL (Biological study)
(**opiate** receptors of brain response to chronic administration of)
RN 16590-41-3 CA
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

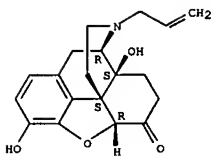
L12 ANSWER 52 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



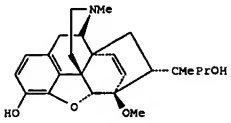
L12 ANSWER 53 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 100:96573 CA
TITLE: In vivo studies on spinal **opiate** receptor systems mediating antinociception. II. **Pharmacological** profiles suggesting a differential association of mu, delta and kappa receptors with visceral chemical and cutaneous thermal stimuli in the rat
AUTHOR(S): Schmauss, Claudia; Yaksh, Tony L.
CORPORATE SOURCE: Dep. Neurosurgical Res., Mayo Clin., Rochester, MN, 55905, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1984**), 228(1), 1-12
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The intrathecal administration of μ (morphine [57-27-2]) and δ (D-Ala2-D-Leu5-enkephalin [63631-40-3]) but not κ agonists (ethylketocyclazocine [36292-66-7], bremazocine [75684-07-0], and U50488H [83913-06-8]) or partial agonists (nalbuphine [**20594-83-6**] and buprenorphine [52485-79-7]) produced a dose-dependent inhibition of all cutaneous thermal (hot plate and tail-flick) responses in the rat. In contrast, on visceral chemical tests (writhing), μ and κ agonists but not δ agonists exerted a powerful suppression of the response. Whereas the ED50 of morphine on the cutaneous thermal tests did not differ from that observed on the visceral chemical test, agents with significant μ and δ activity (metkephamid [66960-34-7] and β-endorphin [60617-12-1]) showed a prominent reduction in activity on the writhing as compared with the hot plate and tailflick. Systemic naloxone [**465-65-6**] resulted in a dose-dependent antagonism of the effect of all intrathecal agents. Estimation of the pA2 of μ agents indicated no difference on the hot plate/tail-flick and writhing (pA2 approx. 7). κ Ligands were selectively resistant to antagonism with naloxone pA2 values for those agonists ranging from 5.9 to 6.6. Apparently, there are 3 discriminable populations of receptors in the spinal cord whose activation results in a **selective** modulation of the response of the animal to noxious stimuli. In addition, the **selective** effects of the δ agonists on cutaneous thermal and κ agonists on visceral chemical stimuli suggest a differential coding of spinal afferents through which these stimuli are transmitted.
IT **465-65-6**
RL: BIOL (Biological study)
(**opiate** receptor of spinal cord in antinociception in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 53 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 54 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 99:63807 CA
TITLE: Interaction of peptides and morphine-like narcotic analgesics with specifically labeled μ- and δ- **opiate** receptor binding sites
AUTHOR(S): Hermans, B.; Gommeren, W.; De Potter, W. P.; Leysen, J. E.
CORPORATE SOURCE: Dep. Med., Univ. Instelling Antwerpen, Wilrijk, B-2610, Belg.
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1983), 263(2), 317-19
CODEN: AIPTAK; ISSN: 0003-9780
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

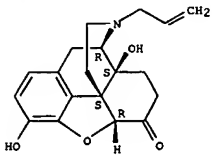


I

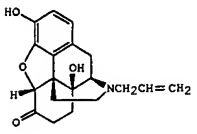
AB In rat forebrain membrane prepns., enkephalin-like peptides revealed high binding affinity and selectivity for δ-type **opiate** receptors; however, syndyphalin [78263-45-3] bound much more potently to μ-type receptor sites. Etorphine (I) [14521-96-1] had high binding affinities for both δ-type and μ-type **opiate** receptor sites. The **opiate** antagonist naloxone [**465-65-6**] and the tricyclic 4-ax-phenylpiperidine ketazocine [36292-69-0] did not differentiate between the receptor types. Tritiated naloxone, particularly when used at 0°, will probably label both μ- and δ-type receptors. However, the lower binding affinity of some narcotics, such as fentanyl [437-38-7], pethidine [57-42-1], and ketazocine for the 3H-naloxone-labeled sites at 0° is probably partly to be attributed to a more marked temperature sensitivity of the binding of these substances as compared to the other **drugs**. Among the **drugs** tested, sufentanil [56030-54-7] displayed the highest binding affinity and the highest selectivity for μ-type **opiate** receptors. Sufentanil appears to be the most **selective** ligand for the μ-type receptor. A correlation between the analgesic activity of **drugs** and their binding affinities for δ-type **opiate** receptors is apparent.
IT **465-65-6**
RL: BIOL (Biological study)
(binding of, by **opiate** receptor subtypes of brain, analgesic activity in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

L12 ANSWER 54 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)

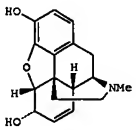
Absolute stereochemistry.



L12 ANSWER 55 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 98:173082 CA
TITLE: Effects of **opiate** agonists and antagonists on fluid intake and saccharin choice in the rat
AUTHOR(S): Cooper, S. J.
CORPORATE SOURCE: Dep. Psychol., Univ. Birmingham, Birmingham, B15 2TT, UK
SOURCE: Neuropharmacology (1983), 22(3A), 323-8
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

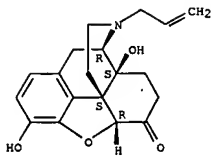


II

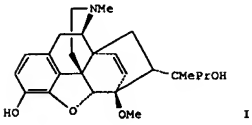
AB Both naloxone (I) [**465-65-6**] (3 and 10 mg/kg) and naltrexone [**16590-41-3**] (1-10 mg/kg) abolished the preference for a highly palatable 0.05% Na saccharin solution in rats that had been adapted to a 22 h water-deprivation schedule. The effect occurred as a result of a **selective** decrease in the consumption of the saccharin solution, since the intake of water, which was concurrently available in the two-fluid choice test, remained unaffected. When a less preferred saccharin solution was used (0.01%), naltrexone exerted a similar suppressant effect on the Na preference, while naloxone failed to produce significant effects on the intake of saccharin solution or water. The data for the **opiate** agonists were interpreted in terms of a **drug**-induced blockade of the natural reward of highly palatable fluids in thirsty rats. In the same choice test, morphine (II) [57-27-2] and a stabilized enkephalin analog, with a **selective** agonist action at μ- **opiate** receptors (RX 783030 [72080-55-8]), failed to influence the preference for the palatable saccharin solns. In water-deprived animals, at least, exogenous **opiate** agonists, active at μ-receptors, did not appear to influence the reward of the palatable solns.
IT **465-65-6**
RL: BIOL (Biological study)
(fluid intake response to, palatability in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 55 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 56 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 98:137156 CA
TITLE: **Opiate** binding sites in bovine retina: evidence for benzomorphan **selective** binding sites
AUTHOR(S): Osborne, Hillman H.; Herz, Albert
CORPORATE SOURCE: Dep. Neuropharmacol., Max-Planck-Inst. Psychiatrie, Munich, D-8000/40, Fed. Rep. Ger.
SOURCE: European Journal of Pharmacology (**1983**), 86(3-4), 373-8
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

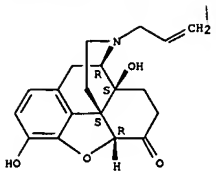


I

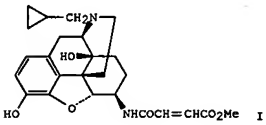
AB The binding of 3H-labeled etorphine (I) [14521-96-1] to **opiate** binding sites in bovine retina was examined in the presence and absence of β-casomorphin-4-NH2 [74135-04-9]. Seventy percent of the **opiate** binding sites in retina were blocked selectively by 10 μM β-casomorphin-4-NH2, probably corresponding to μ-**selective** binding sites; no evidence was obtained for δ-binding sites. The residual (30%) binding sites were **selective** for benzomorphan **drugs** which exhibited Ki values in the 20-40 nM range. μ-Agonists and δ-agonists displayed a weak affinity to benzomorphan sites, with Ki values in the range 200 nM-10 μM.
IT **465-65-6**
RL: PROC (Process)
(binding of, to retina receptor)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 56 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 57 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 98:83123 CA
TITLE: Improved assays for the assessment of κ- and δ-properties of opioid ligands
AUTHOR(S): Ward, Susan J.; Portoghese, P. S.; Takemori, A. E.
CORPORATE SOURCE: Coll. Pharm., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: European Journal of Pharmacology (**1982**), 85(2), 163-70
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

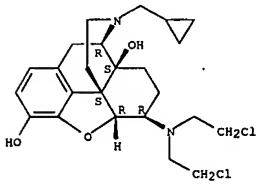


I

AB The highly **selective** non-equilibrium μ-antagonist β-funaltrexamine (β-FNA)(I) [**72782-05-9**] produced a maximal 20-fold shift in the IC50 for the μ-agonist morphine [57-27-2] on the guinea pig ileum preparation, whilst producing no significant change in the IC50 for the κ-agonist ethylketazocine [36292-66-7]. On prepns. pretreated with β-FNA, the pA2 values for the interaction of morphine and ethylketazocine with naloxone were similar. These values were similar to the pA2 value for the interaction of ethylketazocine and naloxone determined on control tissues, but significantly different from the pA2 value for morphine-naloxone on control tissues, indicating that the agonist actions of morphine on prepns. pretreated with high concns. of β-FNA are mediated by κ-, rather than μ-receptor interaction. On the mouse vas deferens preparation, co-incubation with the highly **selective** δ-agonist Tyr-D-Ser-Gly-Phe-Leu-Thr (DSLET) [75644-90-5] and the non-**selective** non-equilibrium **opiate** antagonist β-chlornaltrexamine (β-CNA) [**67025-94-9**] resulted in marked inhibition of the agonist actions of morphine but had no effect upon the agonist actions of the δ-agonist leucine-enkephalin [58822-25-6]. The pA2 values for the interactions of naloxone with leucine-enkephalin and etorphine [14521-96-1] were unaltered by pretreatment with β-CNA and DSLET. In similarly pretreated tissues, the agonist actions of ethylketazocine were markedly inhibited. The guinea pig ileum and mouse vas deferens prepns. treated in this manner results in assay systems that possess a largely homogeneous receptor population, and as such are valuable tools with which to evaluate opioid activity.
IT **67025-94-9**
RL: BIOL (Biological study)

L12 ANSWER 57 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
(**opiate** receptor response to, detn. of)
RN 67025-94-9 CA
CN Morphinan-3,14-diol, 6-[bis(2-chloroethyl)amino]-17-(cyclopropylmethyl)-4,5-epoxy-, (5α,6β)- (9CI) (CA INDEX NAME)

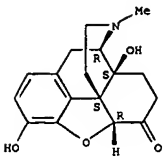
Absolute stereochemistry.



L12 ANSWER 58 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 98:361 CA
TITLE: The binding spectrum of narcotic analgesic **drugs** with different agonist and antagonist properties
AUTHOR(S): Magnan, Jacques; Paterson, Stewart J.; Tavani, Alessandra; Kosterlitz, Hans W.
CORPORATE SOURCE: Marischal Coll., Univ. Aberdeen, Aberdeen, AB9 1AS, UK
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1982), 319(3), 197-205
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four groups of narcotic analgesic **drugs** were assessed for their **opiate** activities in 3 binding assays and 3 **pharmacol.** bioassays. In the binding assays, inhibition consts. were determined against the binding of a μ-, δ-, and κ-ligands. The **pharmacol.** agonist or antagonist activities were assayed on the guinea-pig ileum, mouse vas deferens and rat vas deferens. The first group of compds. were pure agonists in all 3 **pharmacol.** bioassays. The majority of the compds. showed preference to μ-binding but phenazocine [127-35-5] and particularly etorphine [14521-96-1] had also high affinities to the δ- and κ-binding sites. The second group consisted of N-allyl and N-cyclopropylmethyl homologs of the morphine, 3-hydroxymorphinan and normetazocine series which had agonist and antagonist activities in the guinea-pig ileum and mouse vas deferens but were pure antagonists in the rat vas deferens. In the binding assay, μ-binding and κ-binding were prominent. The third group was made up by the ketazocine-like compds. which in the guinea-pig ileum and mouse vas deferens were pure agonists and in the rat vas deferens pure antagonists. The binding spectrum showed particularly high binding to the κ-binding site. The fourth group was the antagonists which were devoid of agonist activity with the exception of diprenorphine [14357-78-9] and Mr2266 [56649-76-4] which had retained some agonist activity. The binding spectrum showed considerable variation, naloxone [**465-65-6**] in low concentration being a **selective** μ-antagonist, Mr2266 having high affinities to the μ- and κ-binding sites and diprenorphine having considerable affinities to the μ-, δ- and κ-binding sites. Since each of the four groups of compds., whether pure agonists, agonist-antagonists, ketazocine-like **drugs** or pure antagonists, shows independent variations in the affinities to the μ- and κ-binding sites, their different **pharmacol.** behavior cannot be solely due to difference in the binding spectra.
IT **76-41-5**
RL: BIOL (Biological study)
(**opiate** μ- and δ- and κ-receptors binding of)
RN 76-41-5 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, (5α)- (9CI) (CA INDEX NAME)

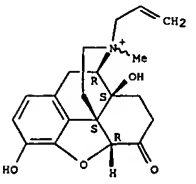
Absolute stereochemistry.

L12 ANSWER 58 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



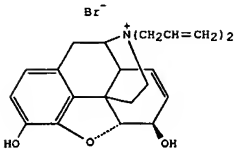
L12 ANSWER 59 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 97:174870 CA
TITLE: Peripheral selectivity of quaternary narcotic antagonists: relative ability to prevent gastrointestinal transit inhibition and antinociception in morphinized rats
AUTHOR(S): Manara, L.; Bianchi, G.; Fiocchi, R.; Tavani, A.
CORPORATE SOURCE: Mario Negri Pharmacol. Res. Inst., Milan, 62-20157, Italy
SOURCE: Adv. Endog. Exog. Opioids, Proc. Int. Narc. Res. Conf., 12th (1981), 402-4. Editor(s): Takagi, Hiroshi; Simon, Eric J. Kodansha: Tokyo, Japan.
CODEN: 48NVAY
DOCUMENT TYPE: Conference
LANGUAGE: English
AB nalorphine allobromide [69576-07-4] Or methobromide [58046-46-1], naloxone methobromide [**73232-49-2**], and naltrexone methobromide [**73232-52-7**] were given s.c. to rats before morphine, 5 mg/kg, i.v. Doses slightly decreasing **opiate** antinociception(central = A) and inducing recovery of gastrointestinal transit to about 50% of **drug**-free rats (peripheral = B) were compared. The A:B index of peripheral selectivity was at least 8 for any of the antagonists given 10 min before morphine, but prolonging this interval variably affected A:B which for naltrexone methobromide ranged from >60 (10 min) to about 1 (80 min). Thus quaternary narcotic antagonists may be useful for **selective** blockade outside the central nervous system of specific action sites of opiates.
IT **73232-49-2**
RL: PROC (Process)
(binding of, to peripheral **opiate** receptors, selectivity in)
RN 73232-49-2 CA
CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, bromide, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br⁻

L12 ANSWER 60 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 97:668 CA
TITLE: Quaternary narcotic antagonists' relative ability to prevent antinociception and gastrointestinal transit inhibition in morphine-treated rats as an index of peripheral selectivity
AUTHOR(S): Bianchi, Giancarlo; Fiocchi, Roberto; Tavani, Alessandra; Manara, Luciano
CORPORATE SOURCE: Lab. Drug Metab., Ist. Ricerche Farmacol. "Mario Negri", Milan, 20157, Italy
SOURCE: Life Sciences (1982), 30(22), 1875-83
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

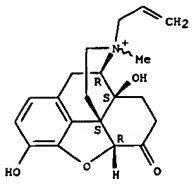


I

AB Single doses of naloxone (0.025 to 0.5 mg/kg) or of 1 of 4 quaternary narcotic antagonists nalorphine allobromide (I) [69576-07-4], nalorphine methobromide [58046-46-1], naloxone methobromide [**73232-49-2**] or naltrexone methobromide [**73232-52-7**] (1 to 60 mg/kg) were given s.c. to rats before morphine, 5 mg/kg, i.v. In the absence of antagonists, morphine reduced gastrointestinal transit of a charcoal meal to about 15% of **drug**-free controls and consistently delayed nociceptive reactions (55° hot plate) in all animals. Doses of antagonists slightly reducing morphine antinociception (centrally effective = A) and restoring gastrointestinal transit to about 50% of **drug**-free rats (peripherally effective = B) were estimated The A:B ratio, indicating peripheral selectivity, was at least 8 for any of the quaternary antagonists given 10 min before morphine, but prolonging this interval may have resulted in a lower figure (i.e. less peripheral selectivity) because of reduced A and increased B. This was definitely so for naltrexone methobromide (A:B, > 60 at 10 min, about 1 at 80 min) and was not apparent for nalorphine methobromide according to available data, which for nalorphine allobromide and to a lesser extent for naloxone methobromide showed only an increase in B at intervals longer than 10 min. Both morphine-induced antinociception and inhibition of gastrointestinal transit were reduced by naloxone at the lower doses tested and were fully prevented at the higher. Apparently, unlike naloxone, the investigated quaternary narcotic antagonists are interesting prototype **drugs** for **selective** blockage of **opiate** receptors outside the central nervous system, although certain critical aspects, possibly biol. N-dealkylation to the corresponding tertiary antagonists, condition peripheral selectivity.

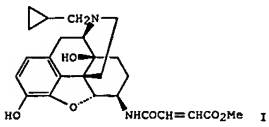
L12 ANSWER 60 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)
IT 73232-49-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(narcotic antagonist activity of, peripheral selectivity of)
RN 73232-49-2 CA
CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, bromide, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br⁻

L12 ANSWER 61 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 96:193311 CA
TITLE: **Pharmacological** characterization in vivo of the novel **opiate**, β-funaltrexamine
AUTHOR(S): Ward, S. J.; Portoghese, P. S.; Takemori, A. E.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Minnesota, Minneapolis, MN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1982**), 220(3), 494-8
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

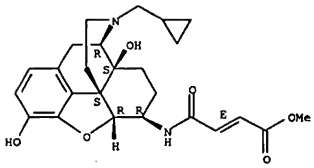


I

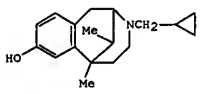
AB The profile of action of β-funaltrexamine (β-FNA)(I) [**72782-05-9**] on antinociceptive tests in vivo was investigated. β-FNA demonstrated antinociceptive actions that were of short duration and that appeared to be mediated by κ-receptor interaction. In contrast, the antagonist actions of β-FNA were of remarkably long duration and were **selective** toward μ-agonist interactions. This profile of action is consistent with the profile of action of β-FNA in vitro. The **selective** long-lasting antagonism of μ-mediated effects by β-FNA may be of great value in the elucidation of multiple opioid receptor function.
IT **72782-05-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(antinociceptive activity of, **opiate** receptor characterization in relation to)
RN 72782-05-9 CA
CN 2-Butenoic acid, 4-[[(5α,6β)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]amino]-4-oxo-, methyl ester, (2E)- (9CI) (CA
INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L12 ANSWER 61 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 62 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 95:197106 CA
TITLE: Demonstration of [3H]cyclazocine binding to multiple **opiate** receptor sites
AUTHOR(S): Zukin, R. Suzanne; Zukin, Stephen R.
CORPORATE SOURCE: Dep. Biochem., Albert Einstein Coll. Med., Bronx, NY, 10461, USA
SOURCE: Molecular Pharmacology (**1981**), 20(2), 246-54
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

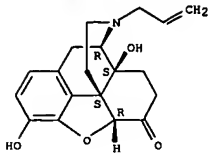


I

AB The binding of 3H-labeled cyclazocine (I) [3572-80-3] to rat brain homogenates was studied. Specific binding, (defined as total binding minus binding in the presence of 10 μM nonradioactive cyclazocine) constituted .apprx. 92% of total binding at 1.0 nM 3H-labeled ligand and 67% of total binding at 100 nM 3H-labeled ligand. Scatchard analyses utilizing various competing **drugs** revealed the apparent interaction of this **drug** with 3 distinct binding sites characterized by affinities of 0.2, 11, and 70 nM (50 nM Tris-HCl buffer, pH 7.4 at 4°). The high- and low-affinity [3H]cyclazocine sites exhibited differential sensitivities to Na and also to the **selective** SH reagent N-ethylmaleimide. In addition, all 3 sites exhibited >50% loss of specific binding following incubation with trypsin (5 μg/mL) for 15 min at room temperature, and >80% loss of specific binding
following incubation at 60° for 15 min in the absence of added reagents. Thus, all 3 sites have a protein-like component. Competition analyses involving rank order detns. for a series of opiates and other **drugs** indicate that the cyclazocine binding sites represent, in order of decreasing affinity, the classical **opiate** receptor (the putative μ receptor), a second as yet uncharacterized **opiate** binding site, and the specific 3H labeled phencyclidine [77-10-1] binding
site. Specific [3H]phencyclidine binding can be displaced by cyclazocine (IC50 = 350 nM) and by related benzomorphans, but not by classical opiates
such as morphine [57-27-2] or naloxone [**465-65-6**]. A common binding site in rat nervous tissue for phencyclidine and some of the benzomorphan opiates is proposed.
IT **465-65-6**
RL: PROC (Process)
(binding of, brain receptor, site in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

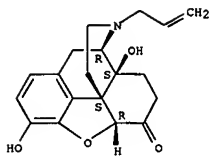
L12 ANSWER 62 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



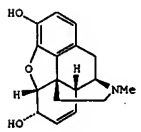
L12 ANSWER 63 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 95:161821 CA
TITLE: Novel **opiate** binding sites **selective** for benzomorphan **drugs**
AUTHOR(S): Chang, Kwen-Jen; Hazum, Eli; Cuatrecasas, Pedro
CORPORATE SOURCE: Dep. Mol. Biol., Wellcome Res. Lab., Research Triangle Park, NC, 27709, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1981), 78(7), 4141-5
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The simultaneous addition of [D-Ala2,D-Leu5]enkephalin [63631-40-3] and morphiceptin [74135-04-9] at concns. at which 98% of enkephalin (δ) and morphine [57-27-2] (μ) receptors are occupied only partially inhibits the binding of 3H-labeled diprenorphine [14357-78-9] to rat brain membranes. These conditions, furthermore, do not affect the curves for displacement of [3H]diprenorphine binding by unlabeled diprenorphine. Apparently, [3H]diprenorphine binds to a third subtype of **opiate** binding site, which has high affinity for diprenorphine but very low affinity for μ and δ agonists. The [3H]diprenorphine binding observed in the presence of morphiceptin and [D-Ala2,D-Leu5]enkephalin exhibits high affinity for several benzomorphan **drugs** in the chemical family of 6,7-benzomorphan (e.g., cyclazocine [3572-80-3], ethylketocyclazocine [36292-66-7], SKF 10047 [14198-28-8], UM 1072 [57203-00-6], oxilorphan [42281-59-4], etc). Because of its selectivity for most benzomorphan **drugs**, this putative receptor site is tentatively referred to as a benzomorphan binding site. Its regional distribution in rat brain is similar to that of morphine (μ) receptors but differs from that for enkephalin (δ) receptors. The content of benzomorphan binding sites in rat brain is only 0.5-0.33 that of morphine receptors. The relative affinities of various opioids to morphine, enkephalin, and benzomorphan binding sites are also described.
IT **465-65-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(benzomorphan binding sites of brain response to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 63 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 64 OF 66 CA COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 93:197652 CA
TITLE: Excitatory and inhibitory effects of opiates in the rat vas deferens: a dual mechanism of **opiate** action
AUTHOR(S): Jacquet, Yasuko F.
CORPORATE SOURCE: Cent. Neurochem., Rockland Res. Inst., Ward's Island, NY, 10035, USA
SOURCE: Science (Washington, DC, United States) (1980), 210(4465), 95-7
CODEN: SCIEAS; ISSN: 0036-8075
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

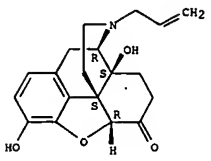


I

AB Both natural (-)-morphine (I) [57-27-2] and its unnatural enantiomer (+)-morphine [65165-99-3] exert an excitatory action on elec. stimulated contractions of rat vas deferens. Preexposure to (-)-morphine results in cross-tolerance to the inhibitory action of β-endorphin [60617-12-1]. (-)-Naloxone [**465-65-6**] and its stereoisomer (+)-naloxone [65700-73-4] also exert an excitatory action, but only (-)-naloxone blocks the inhibitory action of β-endorphin. Thus morphine exerts a dual action on a peripheral organ: one an inhibitory action mediated by the stereospecific endorphin receptor that is blocked stereospecifically by naloxone, the other an excitatory action mediated by a nonstereospecific receptor that is not blocked by naloxone. The **opiate** abstinence syndrome is seen as due to the unmasking of the excitatory action of opiates when its concomitant inhibitory influence is removed by **selective** blockade by naloxone or weakened by **selective** tolerance. The view that the rat vas deferens is devoid of morphine receptors is now seen as arising from a reverse example of morphine's dual action: the masking of the inhibitory action of morphine by its concomitant and more potent excitatory action.
IT **465-65-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(vas deferens response to, **opiate** receptor in relation to)
RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)-(9CI) (CA INDEX NAME)

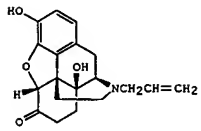
Absolute stereochemistry.

L12 ANSWER 64 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 65 OF 66 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 88:130674 CA
TITLE: [3H]Opiate binding: anomalous properties in kidney and liver membranes
AUTHOR(S): Simantov, Rabi; Childers, Steven R.; Snyder, Solomon H.
CORPORATE SOURCE: Dep. Pharmacol., Johns Hopkins Univ. Sch. Med., Baltimore, MD, USA
SOURCE: Molecular Pharmacology (1978), 14(1), 69-76
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

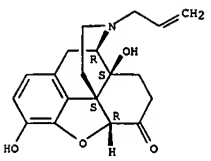
AB 3H-labeled naloxone (I) [465-65-6] and dihydromorphine [509-60-4] were bound by membrane fractions of guinea pig kidney and liver in a saturable fashion and with high affinity. Binding in guinea pig kidney displayed reversed stereospecificity, with the pharmacol .inactive dextrallorphan [5822-43-5] being more potent than the known pharmacol. active levallorphan [152-02-3]. Opiate agonists tended to be more potent than their corresponding antagonists in competing for 3H-labeled opiate binding in guinea pig kidney. Unlike brain opiate receptors, in which Na and Mn selectively decreased and increased, resp., the binding of 3H-labeled opiate agonists, these ions had no selective effect on the binding of 3H-labeled opiates in guinea pig kidney and liver. The opioid peptides Met-enkephalin [58569-55-4] and β-endorphin [60617-12-1] and the opiates etorphine [14521-96-1] and diprenorphine [14357-78-9], which have very high affinity for brain opiate receptors, had negligible effects on 3H-labeled opiate binding in guinea pig kidney.

IT 465-65-6
RL: PROC (Process)
(binding of, to kidney and liver membranes)

RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 65 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



L12 ANSWER 66 OF 66 CA COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 83:201968 CA
TITLE: Mechanism of the synaptic effects of morphine, indomethacin, and prostaglandins
AUTHOR(S): Ehrenpreis, Seymour; Greenberg, Joel
CORPORATE SOURCE: New York State Res. Inst. Neurochem. Drug Addict., New York, NY, USA
SOURCE: Clin. Pharmacol. Psychoact. Drugs, [Proc. Int. Symp. Alcohol Drug Res.] (1975), Meeting Date 1973, 171-82. Editor(s): Sellers, E. M. Alcohol. Drug Addit. Res. Found.: Toronto, Can.
CODEN: 31QKAO
DOCUMENT TYPE: Conference
LANGUAGE: English
GI For diagram(s), see printed CA Issue.

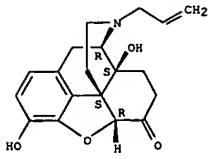
AB In the elec. stimulated guinea pig ileum morphine (I) [57-27-2] blocks transmission by inhibiting release of acetylcholine [51-84-3]; naloxone [465-65-6] antagonizes the block by competing for the morphine receptor ("T" receptor). Naloxone also causes a contracture of the tissue when added after morphine. This contracture results from displacement of morphine from a 2nd receptor ("I" receptor) which may be on the synaptic vesicle. This effect may account for some of the symptoms observed during precipitated withdrawal. Evidence is presented to implicate the "I" receptor in tolerance; the "T" receptor may correspond with the CNS central nervous system receptor responsible for analgesia. Prostaglandins (PGs) of the E series selectively reverse block of transmission by morphine and other opiates and it is suggested that the "T" receptor is actually a prostaglandin receptor. It is proposed that PG acts as a modulator of acetylcholine transmission in the ileum. This was confirmed by the finding that indomethacin [53-86-1], an inhibitor of PG synthesis, blocks transmission; this effect is reversed by very low concns. of PGE1 [745-65-3] or E2 [363-24-6]. This occurs whether the tissue is exposed to indomethacin in vitro or if the drug is injected. Thus it is proposed that the central effects of morphine and other analgesics are produced by the selective inhibition of cholinergic transmission. These drugs have little if any effect on adrenergic transmission, for example in the vas deferens.

IT 465-65-6
RL: BIOL (Biological study)
(acetylcholine release by intestine response to morphine in relation to)

RN 465-65-6 CA
CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L12 ANSWER 66 OF 66 CA COPYRIGHT 2005 ACS on STN (Continued)



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L2              50 S L1 SAM
L3            2409 S L1 FULL

     FILE 'CA' ENTERED AT 15:11:24 ON 15 SEP 2005
L4            8979 S L3

     FILE 'REGISTRY' ENTERED AT 15:11:44 ON 15 SEP 2005
L5             STRUCTURE UPLOADED
L6            2397 S L5 FULL

     FILE 'CA' ENTERED AT 15:12:50 ON 15 SEP 2005
L7            8977 S L6
L8            7759 S L7 AND PY<2002
L9           14184 S OPIATE
L10           2370 S L8 AND L9
L11            170 S SELECTIVE AND L10
L12             66 S L11 AND (PHARM? OR DRUG?)

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STN INTERNATIONAL LOGOFF AT 15:14:19 ON 15 SEP 2005
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